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ANNALS OF INTERNAL MEDICINE

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NUMBER 1

SOME EXPERIMENTAL OBSERVATIONS PERTI- NENT TO THE TREATMENT OF HEPATIC DISEASE*

By JESSE L. BOLLMAN, M D, *Rochester, Minnesota*

OUR fundamental knowledge of the functions of the liver is based on physiologic studies of that organ. We have learned from observation of animals after complete removal of the liver that this organ is essential for the maintenance of the sugar of the blood. Jaundice develops in hepatectomized animals, but the liver is necessary to convert bilirubin which reacts indirectly to the van den Bergh test to direct reacting bilirubin.

Many other metabolic processes have been shown to be entirely dependent on the liver¹. Such functions are but rarely found to be materially impaired in the presence of hepatic disease as seen clinically. Explanation of the adequacy of these fundamental hepatic functions in the presence of extensive hepatic disease is afforded by experiments which show that more than 80 per cent of the liver can be removed from animals without demonstrable impairment of these functions. Further explanation is afforded by the fact that regeneration of the liver occurs rapidly after its partial removal or destruction by toxic agents. It should be noted also that hepatic regeneration is inhibited by the presence of jaundice, continued administration of hepatotoxic agents, or by a reduction of the blood supply to the liver².

Studies in experimental pathology of acute, subacute and chronic hepatic degeneration produced by toxic agents such as carbon tetrachloride appear to show many similarities to hepatic disease as it occurs in human beings. Most of the experimental conditions can be clearly defined, and definite factors can be shown to influence the development and course of experimental lesions. While our knowledge of hepatic disease, both clinical and experimental, is not sufficiently complete to warrant dogmatic application of experimental observations to the treatment of hepatic disease, the factors which may be shown to influence experimental hepatic lesions should indi-

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cate general principles applicable to the treatment of disease of the liver in human beings

Most of the observations which I will discuss were made on dogs which were given carbon tetrachloride, either by stomach tube or by inhalation. An overwhelming amount of this drug produces deep narcosis and immediate death from respiratory failure. With small doses, acute necrosis of the liver occurs, the extent of which may vary with the amount of the drug administered and be greatly influenced by the nutritive condition of the animal at the time the drug is given. Several hours after administration of carbon tetrachloride, the animal loses its appetite and emesis may occur. Jaundice is usually evident on the second day, and the animal becomes more stuporous until death occurs. If the animal survives beyond three or four days, complete recovery usually occurs. During the first few days extensive necrosis and fatty changes take place in the liver, but complete repair occurs within about two weeks and the liver appears almost normal histologically. Repeated administration of carbon tetrachloride at intervals of less than two weeks produces more chronic lesions of the liver, similar to those found in portal types of cirrhosis. After several months ascites, bilirubinemia, collateral circulation and other evidences of cirrhosis are present, and unless the course is altered such animals die from hemorrhage into the gastrointestinal tract or from a gradually progressing toxemia associated with a more or less stuporous condition.

The size and chemical composition of the liver may be greatly varied in normal animals by adherence to an unbalanced diet. Large differences ensue, especially in the glycogen, fat and water content of the liver, depending on the excess or deficiency of carbohydrate, fat, or proteins in the diet. Except when extreme conditions obtain, the ordinary functioning capacity of the liver does not appear to be disturbed. When additional stress is placed on the liver, as by the repeated administration of carbon tetrachloride, differences in function become apparent. The difference is clearly illustrated in the following experiment. Sixteen dogs, of approximately the same size, each received 10 cc of carbon tetrachloride by mouth daily for the duration of the experiment. Four were maintained on a diet containing about 90 per cent carbohydrate, four received a mixed diet of approximately 50 per cent carbohydrate and 25 per cent each of protein and fat, four received lean meat only, and four received a diet consisting of 80 per cent fat and 10 per cent each of carbohydrate and protein. At the end of three weeks all four of the fat-fed animals were dead. Necropsy revealed each to be icteric, the liver appeared enlarged and fatty, and numerous areas of degeneration were present in sections of the liver. At the end of one month one of the meat-fed animals had marked ascites and died two weeks later. Within three months another of the meat-fed animals died with marked ascites and the other two had definite ascites but otherwise appeared to be in good condition. In the same period the other eight dogs remained in good condition and showed no signs of ascites. Biopsy specimens of the

liver of the meat-fed animals at the end of three months disclosed that they had suffered more extensive injury than was present in the other animals, although all showed some evidence of early cirrhosis. In six to eight months the hepatic lesions of the other animals appeared about the same as those of the meat-fed animals at three months.

The effects of alcohol in the production of experimental cirrhosis are less clearly defined. We have given alcohol to the stage of definite intoxication to dogs twice daily for more than two years. Those animals which took a well-balanced diet during this time showed no gross or microscopic hepatic abnormalities. In animals receiving carbon tetrachloride and alcohol, acute hepatic degenerative changes developed rapidly and cirrhosis developed with less carbon tetrachloride than was necessary without the alcohol. We had interpreted this effect as perhaps being due to the greater solubility of carbon tetrachloride in alcohol, with the consequent more rapid absorption of effective amounts of carbon tetrachloride, but we have recently altered this view because of new evidence regarding the effect of alcohol on the liver. Alcohol in the presence of an adequate diet produces no demonstrable effect on the liver, but when food is withheld or when diets predominantly fat are given with the alcohol, the liver rapidly becomes fatty. With a fat diet that would produce fatty livers in dogs in from six to eight weeks, the addition of alcohol causes the liver to become fatty in two or three days. It is quite probable that alcohol may in a like manner increase the susceptibility of the liver to other toxic agents.

We have called attention to the fact that on examination of animals which have died from extensive hepatic injury, regardless of the methods by which it was produced, the investigator does not find the typical symptoms or the chemical changes that are found following complete removal of the liver.³ The detoxicating function of the liver appears to be depressed by changes in the organ so that the susceptibility to toxic agents is responsible for the symptoms shown, and usually the animal succumbs before the entire function of the liver is lost. When the toxic agent has destroyed part of the liver, some of the toxic substances present may be of metabolic origin and are somewhat related to the autolytic disintegration products of injured hepatic tissue. These considerations seem particularly applicable to animals with hepatic lesions which do not appear to be very detrimental to the animal under ordinary conditions but which cause it to fail rapidly following a surgical procedure which would be of no consequence to a normal animal. Following operation, these animals are markedly lacking in resistance, and extensive degenerative changes may rapidly occur in the previously injured liver.

That the condition of the liver may alter the effect of various toxic agents can be shown in a number of ways. Intoxication with alcohol may be produced in dogs with fatty livers by half the amount required to produce the same degree of intoxication in normal animals. Anesthesia with the various barbiturate derivatives is produced with about half of the amount

necessary for normal animals. The immediate effect of carbon tetrachloride is also greatly increased and the extent of hepatic damage produced is greater. In each of these examples the response to the toxic agent is similar in quality, but the quantitative response is greater the more the liver is impaired.

From an experimental standpoint certain measures have been shown to be of value in combating the fatal toxemia that follows the administration of hepatotoxic agents. The prophylactic value of diets containing large amounts of carbohydrate has been mentioned, and in combating the acute toxic effects of hepatotoxic agents, the administration of carbohydrates is of definite value. Since food is seldom taken when the animals are acutely ill, glucose given intravenously has seemed to us to have been a life saving measure when animals would otherwise have died of acute carbon tetrachloride poisoning. It is not certain just what part in maintaining the animal is played by the glucose and how much should be attributed to the fluid administered and the maintenance of renal function. Examples of the influence of carbohydrate in the diet with continued administration of carbon tetrachloride have been given. The prolonged maintenance of animals following complete biliary obstruction by means of diets rich in carbohydrate is also worthy of notice.

We have not been able to produce cirrhosis in dogs by the administration of carbon tetrachloride to the extent that ultimate symptomatic (and in part anatomic) recovery was impossible when administration of the drug was discontinued. The signs and symptoms noted in animals after the development of cirrhosis appear to be attributable to the summation of acute changes produced by carbon tetrachloride and are not immediately associated with the more permanent scarring and nodular formation in the liver. If administration of the drug is discontinued when dogs have such extreme symptoms as jaundice, emaciation and rapid accumulation of ascitic fluid, and when many tests considered as indicative of extreme damage to the liver are positive, the animals gave definite evidence of improvement within a few weeks. Within two to six months after discontinuation of the administration of carbon tetrachloride and under maintenance on a diet rich in carbohydrate, all symptoms of cirrhosis disappear, the only evidence of previous hepatic injury that persists being the collateral circulation and the appearance of gross and microscopic distortion of the hepatic lobules. Animals may then be maintained on any adequate diet, bilirubinemia is absent, ascites is absent, and there is no symptomatic or chemical change indicative of hepatic abnormality. With all tests that we have used which are considered as being tests of liver function, the reaction has approached that of the normal animal.

The occurrence of ascites in experimental cirrhosis is associated with alterations in the protein content of the serum, and the level of the serum proteins at which ascites occurs appears to be inversely proportional to the extent of hepatic damage. We have not observed ascites in cirrhotic dogs

when the serum proteins were normal. Usually there is a reduction in the total proteins of the blood, most of the decrease being due to the lowered albumin content. The plasma globulin is usually increased in respect to the albumin content and is frequently found to be present in amounts greater than that found in normal animals. The withdrawal of plasma protein by plasmapheresis hastens the onset of ascites and the lowering of the plasma proteins with the foregoing changes in composition. The regeneration of plasma proteins is less rapid when the liver is damaged but, as in the normal animal, is somewhat dependent on the proteins of the diet. The regeneration of plasma proteins in cirrhotic animals receiving a diet rich in protein is much greater than in similar animals receiving only small amounts of protein in the diet. The more rapid regeneration of plasma proteins, which occurs when the condition of the liver is improved, is more effective than the regeneration obtainable from diets rich in protein.

REFERENCES

- 1 BOLLMAN, J. L. and MANN, F. C. The physiology of the impaired liver, *Ergebn d Physiol*, 1936, **xxxviii**, 445-492
- 2 MANN, F. C., FISHBACK, F. C., GAY, J. G., and GREEN, G. F. Experimental pathology of the liver studies III, IV, and V, *Arch Path*, 1931, **xii**, 787-793
- 3 BOLLMAN, J. L., and MANN, F. C. Alterations in hepatic function produced by experimental hepatic lesions, *Ann Int Med*, 1935, **ix**, 617-624

CLIMATE, MODE OF LIFE, AND HEART DISEASE¹

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ARM chair philosophy in medicine has its place, but without rich experience and wisdom it can play but a minor rôle, it is wise to spend less time discussing our impressions and more time in testing their real truth

In the field of heart disease we have been notably backward in studying carefully the results of nature's own experiments on man the world over. These clues to knowledge await us everywhere. Let me ask you some of the questions that are crying for solution.

Is it really true that coronary disease, especially early atheroma and thrombosis, is becoming more and more common among the young, well-fed, physically indolent, heavy smokers in our northern cities while it passes by the young and middle-aged hard-working farmers and laborers the world over? Is it most prevalent among Hebrews?

Let me interpolate here a question about the effect of tobacco, a topic of perennial interest. Raymond Pearl¹ recently found that heavy smokers live shorter lives than non-smokers but can we blame the tobacco itself necessarily for this? Isn't it just as probable that persons who are intemperate in the use of tobacco are more likely to be intemperate in other respects as well, thereby jeopardizing their health?

Is it simply so-called wear and tear that is responsible for the increasing mortality of our young and middle-aged men from coronary disease, or are there not other causes, at present obscure, that in some manner result from the modern way of life? Why is it that under the age of 40 years the incidence of coronary disease is twenty-four times greater among males than among females?

Does it really harm the arteries to eat diets rich in cream and butter and eggs, no matter what the age or nutritional state? Are we perchance over-feeding our youth in the course of developing a new generation of robust girls and boys? Are we swinging too far from the true and fancied evils of undernutrition in our routine diets of adult life, particularly for sedentary workers? Would it not be wise to return to an occasional fast day? Should not man earn his food physically?

Does regular and adequate exercise really promote health and prolong life as the ancients taught, as theory suggests, and as some of us believe, or is that idea another old wives' tale?

Is it not the loss of muscle tone and of active metabolism rather than the inhalation of exhaust gases that is a pernicious result of our excessive use of motor cars today? Would not our hearts and our brains and our stomachs, as well as our muscles and pocketbooks and city streets benefit by the resumption of the use of our legs either in walking or in cycling, with

* Read before the American College of Physicians, New York, April 5, 1938

the relegation of our motor cars to special occasions when it is really necessary or advisable to use them?

Is it really true that high blood pressure is rare or even nonexistent among the Negroes in Central Africa while it is commoner among the Negroes in our Southern states than in any other group of people in the world? How much hypertension is there among the native Chinese, Arabs, Vermont farmers, New York brokers, Canadian trappers, and Esquimaux?

Does syphilitic aortitis vary in incidence fifty-fold in different communities in various parts of the world?

Is it really true, as many now believe, that the rheumatic infection and mitral stenosis, so common with us, are practically unknown in the tropics?

Is not our stimulating northern or so-called temperate climate actually favorable in its effect on our heart and arteries as well as on our muscles and mental processes, provided we avoid some of its associated evils of over-eating, overwork, and crowding the days and nights through fear that we are missing something that others are doing? Is not such a climate really an asset if we exclude the rheumatic involvement of the heart and these other handicaps I have just cited? Is it necessary to live on a tropic island to be contented and healthy? How often one hears the lament of an overtired man or his wife about the strain of our climate. Is this not simply an unjust accusation due to the unsatisfactory adjustment of life to the many demands of business, profession, family, cultural education, entertainment, sport, and social engagements which crowd every waking hour? Is it not our fault, rather than that of the climate, if high blood pressure and coronary disease and neurocirculatory asthenia and neuroses, cardiac or otherwise, assail us in early life or in middle age?

Was not Ray Lyman Wilbur² right when he recently wrote as follows "Most people have but little idea of how to care for their bodies, or use their brains or be well enough to be happy. The doctors themselves are not always good examples, and many of them care for their automobiles better than they do for themselves." In line with what Dr. Wilbur wrote it has become common knowledge that the physicians are often the earliest victims and the greatest sinners in these very things which they are trying to prevent and to control among their patients. The community at large and often even the doctors themselves do not always appreciate the heavy strain that is shouldered with seeming nonchalance by the doctor who deals all day long with the ills of humanity, spiritual and mental as well as physical. The actively practising physician requires more real leisure for the maintenance of his own good health than do most other individuals in professional and business life. A healthy personal program with ample sleep and exercise does not fit the present scheme of demands, professional and social, on the busy doctor of today. It must in some way be made to fit, for the health of the doctor is truly one of the important problems which face the medical profession in this country.

Let me ask you one more question, an ever intriguing one. What in-

fluence does the weather have in any given climate on the incidence of heart disease or on the symptoms thereof? May not the weather be too stable for the maintenance of a perfect circulation? Can one blame heart disease or heart attacks on low barometric pressure or on high, on high humidity or on low, on too much wind velocity or on too little, on too little rainfall or on too much, on too cold a day or on too hot? Attempts in this direction have been made, for the most part unsuccessfully, since ancient days. I myself realized the almost hopeless tangle and confusion, except in rare cases, when I tried with Dr Brasil to make a preliminary analysis a few years ago of the relationship of acute illness and death among my cardiac patients to the multitudinous weather factors alone and in various combinations. There are to be sure a few simple observations that are well known, chiefly that of the production of angina pectoris by walking against a cold wind, but the great majority of the other correlations are almost pure guesses, and naturally so, in view of the interplay of a host of other factors besides the many of the weather acting on any one patient at any given moment. There are too many variables that are more important than the weather variables themselves to draw many conclusions in the present state of our knowledge. To our surprise, for example, we found that our cases of acute coronary thrombosis occurred more or less uniformly throughout the year with little or no regard to heat or cold, sun or rain, wind or calm, there may have been some intricate or hidden effect of weather, but it will take years of carefully controlled investigation of thousands of cases to unravel them. It may be that the sunspots, aurora borealis, and position of the constellations have a bearing on heart disease and some day it may be so shown, but for the present at least and for the immediate future it appears to be more profitable to study the more potent factors of the mode of life, diet, work, infection, familial and racial inheritance, and climate in general in their bearing on heart disease.

Are there any adequate answers to the important questions I've asked? No. We have our impressions from years of practice or observation, there are meager statistics on certain points here and there, and we have had hopes of studying the problems more intensively. But actually little has been done. In 1934 I attended the triennial congress of the International Association of Geographic Pathologists in Holland. The subject was arteriosclerosis. Many of the world's leaders in pathology and in vascular disease were present but the results were most disappointing. There was but the vaguest idea of the incidence of arteriosclerosis throughout the world. The same thing would probably be true of hypertension, rheumatic valvular disease, and luetic aortitis if there were now to be held international meetings on these subjects.

I have looked through such an extensive survey as McKinley's *Geography of Disease* (1935) ³ based on official health records from all parts of the world but there is disappointingly little about the etiological factors behind heart disease, although much about the great scourges of days past

—tuberculosis, typhoid, and malaria There are to be sure some interesting estimates to speculate about, but it is obvious that careful study is still needed almost everywhere to feel at all sure about the general incidence of various etiological factors, leaving out of consideration altogether the relative incidence among various different groups in any community In Hawaii, for example, rheumatic fever is said to be rare while valvular lesions are noted as common, is that because luetic aortitis is a frequent occurrence or is it because the rheumatic infection escapes notice? Hypertension and cardiovascular disease are said to be common in Hawaii, are they related, or is there also a lot of coronary disease there? On the other hand in the Philip pines in 1934 rheumatic fever was blamed for 318 deaths, one-third as many as all the deaths from cardiovascular disease in that year, can we feel sure about that ratio? In Puerto Rico in 1933 hypertension was noted as common and valvular heart disease as rare, while in Uganda in that same year only three cases of hypertension were noted as against 485 of valvular disease, if these figures are reliable, what is the reason for such differences? In China in 1934 rheumatic fever was reported as rare in the north and common in the center and south, the opposite of our findings in the United States, is this true? Coronary disease, one of the most important of all factors, is barely mentioned in any of the statistics

Dr Takahashi of the Imperial Household in Tokyo kindly sent me the Japanese Health Report for 1934 ⁴ I was especially interested in the diagnosis of coronary disease as a cause of death in the various age groups, between 30 and 40 years of age and between 70 and 80 it was responsible for about $\frac{1}{2}$ per cent of the deaths, between 40 and 70 quite uniformly for about 1 per cent, and after 90 years for less than $\frac{1}{10}$ per cent In the United States, on the other hand, the vital statistics for the same year 1934 gave the diagnosis of coronary disease or angina pectoris as a cause of death in a much higher percentage of cases, thus nearly 2 per cent between the ages of 30 and 40, 4 per cent between 40 and 50, over 6 per cent between 50 and 70, 5 per cent between 70 and 80, and only $\frac{2}{10}$ per cent after 90 Is it really true that in the very important age period between 50 and 70 coronary disease kills relatively six times as many persons in the United States as in Japan? If so, what is the reason? It is not to be ascribed to a disproportion of the mortality by decades in the two countries, for the total mortality runs parallel in the United States and Japan, being greatest in each country between 70 and 80 and next greatest between 60 and 70

Incidentally Dr Takahashi told me that it was his conviction that hypertension had increased very much in Japan in the last two decades, this increase he ascribed to the introduction of the occidental mode of life Meanwhile beri-beri has become relatively rare

A good deal of analysis of the relative incidence of the types of cardiovascular disease in the more advanced parts of the world has been made and they are already worthy of comparison but we are still largely ignorant of the absolute incidence and of the situation among various groups in any one

community—a very vital point Dr Cossio of the Argentine has just sent me some interesting data concerning 4,000 cardiac patients which he has analyzed and also some impressions concerning the community incidence Of the 4,000 cases he has labelled 22 per cent as functional in comparison with 20 per cent of 3,000 cases which we studied in New England,⁵ 22 per cent he called coronary in contrast to 28 per cent of our own, 20 per cent of the Argentine group were hypertensive compared with 24 per cent in New England, only 14 per cent were rheumatic in contrast to our largest percentage of 32, 6 per cent were luetic which is twice the percentage that we found, and the balance of 16 per cent included congenital and thyrotoxic cases, the cor pulmonale, bacterial endocarditis, trauma, and so forth, compared with 10 per cent of our group This interesting comparison between the United States and the Argentine Republic is a beginning, but really only the first step, in the solution of the problem Dr Cossio goes on to say a word or two about the more important aspects of the question He finds, for example, as we do, that rheumatic heart disease is more frequent in hospital than in private practice, that arterial hypertension is more frequent in the city workers and big business men than in the farmers and camp workers, and that rheumatic fever is more common in the cold damp parts of the country than in the warm or cold dry parts

Finally, I have written to various other reliable workers in near and distant parts of the world for statements as to their knowledge or impressions of the incidence of cardiovascular disease in their countries and particularly in different groups in their own communities All have responded in a most cooperative way, expressing their great interest in the subject which they regard as of fundamental importance, but at the same time they disclaim any accurate knowledge Their impressions, however, are often illuminating and pave the way for further study Let me read you a few sentences from the reply of one of these collaborators of mine, Paul Harrison, who is in charge of the American Mission Hospital at Muscat on the Persian Gulf, it is characteristic and to my mind especially illuminating as suggestive of the relatively low incidence of heart disease among the coastal and desert peoples of eastern Arabia He writes "I cannot discuss the questions you put in the way I wish I could We live in a subtropical area here with the heat in the summer fairly extreme, and the humidity at times very high, the sea being next door At times, and in fact usually, our air is dry, for our rainfall is extremely low, under four inches rather than above, on the average Years vary I have seen as high as six This year we have not yet had a quarter of one inch and the usual season for rain is over Last year I doubt if we reached an inch

"Living conditions in our so-called cities are not significantly different than in the somewhat smaller outlying villages which house the date gardeners Malaria is the common disease, and is nearly universal It has

* There is a slight discrepancy in the figures in that Cossio's add up to 100 per cent and ours to 117 per cent because we included cases showing multiple diagnoses in the separate categories

the expected result of large spleens and anemia. Hours are long and the work laborious, inasmuch as labor saving machines are nearly unknown. On the other hand the mental tension is low and nobody takes his work to bed with him.

"The remarks above apply to the oasis dwellers who constitute, I imagine, three-quarters of our population, i.e. the population of the province of Oman. In addition there are the nomads whom we term Bedouins. These are goat raisers of a very limited type. The Bedouins suffer very little from malaria.

"With this much of an introduction it is easier to say what we can of the various problems you mention. The stethoscope and the sphygmomanometer are what we have to work with. Of the four types which you mention (coronary, hypertensive, rheumatic, and luetic) hypertension seems very rare. We see less than a case a year on the average. It is not easy to express any opinion as to whether the rural or urban communities are most affected.

"Heart disease due to syphilis is commoner than hypertension. It is a disease of the coast communities and of the oases, not so much of the Bedouins. Of severe aortic insufficiency we see about a case a year. The Bedouins while suffering from syphilis very widely have developed a distinctly attenuated type. The cardiovascular system is practically never affected. The ports are full of syphilis which has been recently imported from the outside world for the Arabs of these port cities are great travellers. My impression is that even in these port cities the severe late syphilitic lesions are much less common than would be expected in the west.

Aneurysms of the aorta come in, but not frequently. In 25 years I have seen three, I believe, one of the arch and two of the abdominal aorta.

"Rheumatic heart disease is commoner than the above. Mitral lesions are at least double the number of severe aortic lesions. The cases that come to us are far advanced. We see two or three cases a year. It is not possible to be certain but I think that the Bedouin community is more or less free from that type of lesion.

"Acute articular rheumatism we see about a half a dozen cases a year. It is usually of a mild type, and it has never been possible for me to demonstrate a murmur developed during the disease. It runs a protracted course, and several joints are usually affected, one after another before the disease runs out. My impression is very definite that this disease is increasing throughout the coast communities where our contacts are considerable.

"Colds are common through this community, especially in the spring and fall when the prevailing weather changes considerably." Finally, Harrison closes with the observation that living conditions and, in a more or less parallel manner, health conditions have been going down grade of late years because of the increasing poverty incident to the drop in the price of their chief export, dates.

Now, what is the answer to all this? It is evident at once that much

hard work remains to be done and must be done. We cannot experiment on man and we cannot always apply animal experiments satisfactorily to man. But we can make use of the many experiments that nature herself is constantly making on man. It will be possible, I am sure, when the work is done, to evaluate the effect of the various individual factors of climate, race, occupation, diet, and disease on the heart. We can have thousands of cases in which all these essential factors will be closely similar except for the one that is under scrutiny at the moment, for example, how do Chinese laborers or English business men react to different climates? How do different occupations affect one racial group in one climate? How do different races react to a certain type of diet or to a disease?

In conclusion, how may this study be carried out? Obviously by well and similarly trained teams, with good equipment and plenty of time, and with the same program of work. It would be most desirable if such a project could be effected by international effort, as by a League of Nations. It might, however, be done sooner and more practically through some foundation which has been already established for the study of disease and the promotion of public health throughout the world. Or it might be accomplished through the initiative or collaboration of universities. In any given country it might be done by the national government but such a study would be incomplete, it might begin in that way, to be sure, but for completion it would be necessary to secure smooth and effective international cooperation. Finally, it might still be the private endeavor of a group of individuals or of a single well-to-do enthusiast who is burning with the desire to be a pioneer in this vital work. Someday it will be done and medical knowledge will thereby be greatly enriched.

BIBLIOGRAPHY

- 1 PEARL, R. Tobacco smoking and longevity, *Science*, 1938, LXXXVII, 216
- 2 WILBUR, R. L. March of medicine, *Science*, 1938, LXXXVII, 199
- 3 MCKINLEY. A geography of disease, George Washington University Press, Washington, D. C., 1935
- 4 The Annual Report of the Sanitary Bureau of the Home Department of the Imperial Japanese Government for the 10th Year of Showa (1935), Tokyo, 1937
- 5 WHITE, P. D., and JONES, T. D. Heart disease and disorders in New England, *Am Heart Jr*, 1928, III, 302

HYPERPARATHYROIDISM SIMULATING OR ASSOCIATED WITH PAGET'S DISEASE, WITH THREE ILLUSTRATIVE CASES

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Generalized *osteitis fibrosa cystica* (von Recklinghausen's disease) and *osteitis deformans* (Paget's disease) were regarded formerly as related variants of a single skeletal disease. This concept, however, proved irreconcilable with subsequent clinical, roentgenologic, biochemical and pathologic observations and the consensus now is that generalized *osteitis fibrosa cystica* and *osteitis deformans* are discrete and unrelated entities¹. Generalized *osteitis fibrosa cystica* has been shown to be due to hyperparathyroidism² whereas *osteitis deformans* is not due to hyperparathyroidism but to unknown, probably local, factors influencing bone metabolism.

A serious difficulty with the prevailing view, however, lies in the increasing number of patients described as presenting both hyperparathyroidism and Paget's disease. Such cases have been variously regarded as representing transition stages from the one disease to the other,^{3, 4, 5} or as illustrating the fortuitous co-existence of both (unrelated) diseases. The former explanation has become increasingly improbable as evidence against the existence of any relation between hyperparathyroidism and Paget's disease has accumulated (table 1), and on the other hand the number of patients reported as presenting both conditions is now too large to be dismissed as mere coincidence.

This interesting group of cases was classified as "hyperparathyroidism simulating (or complicated by) Paget's disease" by Albright, Aub and Bauer,^{1d} who reported two cases. Our own observations consist of clinical, roentgenologic and biochemical studies on three similar patients with proved hyperparathyroidism presenting, in addition, certain aspects of Paget's disease. We wish to consider here the problems in interpretation and management raised by these patients in relation to the relevant cases in the literature.

CASE HISTORIES

Case 1 A G, an American housewife, aged 51, was admitted to the Urological service of the Presbyterian Hospital in March 1931 for investigation of the genitourinary tract because of intermittent pyuria. She had been well until 1928, when she complained of weakness, loss of 20 pounds and pain in the left flank and lower abdomen, with cloudy urine. In March 1930 the left kidney had been removed at another hospital because of nephrolithiasis with secondary pyonephrosis. Following this operation, she gained weight and felt improved, but weakness persisted. "Arthritic" pains developed in the left hip, lower back and right knee shortly thereafter, and became progressively worse. The urine again became cloudy.

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At the time of admission to the Presbyterian Hospital, physical examination was essentially negative, apart from obesity, except for a moderately enlarged, non-tender right kidney. The urine showed a heavy trace of albumin and many pus cells. The right ureter was catheterized, yielding a steady flow of cloudy urine. Pyelograms revealed a staghorn calculus in the right kidney pelvis, with some dilatation of the pelvis and calices. The lower spine and the pelvis were visualized on these films and appeared to be normal. The blood urea nitrogen was 17.5 mg per cent. The blood Wassermann test was negative. The patient was discharged 10 days after admission, since further surgical intervention was felt to be inadvisable.

She continued to attend the urological service as an out-patient. Lavage of the renal pelvis and various urinary antiseptics during this period failed to control the pyuria. Because of continued diffuse "arthritic" pain and stiffness in the knees,

TABLE I

Resume of Clinical, Roentgenologic and Biochemical Findings in 150 Cases of Hyperparathyroidism and in 147 Cases of Paget's Disease,* with the Essential Pathologic Changes in These Diseases

	Hyperparathyroidism		Paget's Disease	
1 Frequency	Primary hyperparathyroidism rare		Not uncommon in persons over 40	
2 Familial incidence	Primary hyperparathyroidism not familial		Exceptional but does occur	
3 Sex distribution				
Males	37		75	
Females	113		72	
	Age at Operation or Death (No Cases)	Age at Onset of Symptoms (No Cases)	Age when Diagnosed (No Cases)	Age at Onset of Symptoms (No Cases)
4 Age distribution				
1-9 yrs	—	2	0	0
10-19 yrs	12	17	0	0
20-29 yrs	20	25	1	3
30-39 yrs	31	40	9	11
40-49 yrs	39	36	29	36
50-59 yrs	32	23	40	43
60-69 yrs	12	7	51	15
70 yrs plus	4	—	17	3
			(36 cases asymptomatic)	
	Major Early Symptoms (No Cases)	Major Subsequent Symptoms and Signs (No Cases)	Initial Symptoms (No Cases)	Major Subsequent Symptoms and Signs (No Cases)
5 Clinical symptoms and signs				
A Skeletal				
Pain back, hips, extremities, head	71	59	50	79
Gross deformities back, extremities, bony swellings extremities, ribs hips	41	53	21	58
Enlargement of skull	0	1	18	35
Difficulty in gait	23	21	6	43
Bedfast	3	27	0	6
Fractures	27	36	7	18
Muscle weakness	21	22	0	4
B Renal				
Polyuria polydipsia	9	12	0	2
Renal colic	9	4	3	1
C Gastrointestinal				
Nausea, vomiting anorexia	12	20	0	1
Epigastric pain	2	5	0	2
D Miscellaneous				
Marked loss of weight	12	25	0	3
Deafness	0	1	6	33
Paresthesias numbness legs	0	2	2	6
			(36 cases asymptomatic)	
6 Blood findings				
Hypercalcemia	Present in 4/5 of cases. Absence usually associated with renal insufficiency causing nitrogen retention and hyperphosphatemia		Absent in uncomplicated cases	

TABLE I—Continued

	Hyperparathyroidism	Paget's Disease
Hypophosphatemia	Present in about $\frac{1}{2}$ of cases Absence usually associated with renal insufficiency in which hyperphosphatemia may occur	Absent
Serum phosphatase activity	Almost always increased in cases with definite skeletal changes usually to 2 to 10 times maximum normal values Not elevated in cases without definite skeletal changes	Almost always increased up to 40 times maximum normal value Level roughly proportional to extent and activity of bone lesions
7 Calcium balance	In negative calcium balance on diets ordinarily adequate, due to increased urinary excretion	Within normal limits
8 Roentgenologic findings	Usually generalized decalcification with one or more bone cysts and grainy mottling of the skull May not be apparent in early or acute cases Occasionally, sclerotic areas due to recalcification Renal calculi in many cases Fractures common Characteristic deformities	Increased density of involved bones usually with coarsely striated trabeculations sometimes densely sclerotic "Cotton-wool" appearance of skull Not generalized but may involve most bones Typical deformities
9 Pathologic findings	One or more parathyroid tumors present Generalized decalcification of bones increased osteoclastic activity occasional osteoclastomata Some new bone formation with increased osteoblasts Marrow fibrosis Occasional brown tumors Bones often soft misshapen	No parathyroid tumors present Some decalcification but new-bone formation irregularly laid down predominates Typical mosaic segments of lamellar bone prominent cement lines

* With the exception of 9 proved cases of hyperparathyroidism from our own records, this summary of 150 cases of hyperparathyroidism is based upon reports in the literature The data are adapted from the analyses of Gutman, Swenson and Parsons¹⁰ and Gutman⁶ Only cases in which one or more parathyroid tumors were found at operation or autopsy, and in which there was definite evidence of parathyroid over-activity are included

The series of 147 cases of Paget's disease is from the records of the Presbyterian Hospital, 1915-1937 The group includes the series of 116 cases of which a more detailed analysis was published elsewhere⁷

back and fingers, she was referred to the Arthritis Clinic in March 1932 Prominent Heberden's nodes and a non-tender swelling of the right knee with crepitus were noted there and a diagnosis of chronic hypertrophic arthritis was made Diathermy gave no relief of pain

Roentgenograms of the genito-urinary tract were repeated in March 1932 These showed no appreciable change since the preceding year An incidental finding on this occasion, however, was "a peculiarity of the architecture of the left innominate bone which suggests *osteitis deformans*" (figure 1a) In April 1932 she tripped and fell upon her right knee, following which pain, swelling and, subsequently, tenderness of the upper end of the right tibia developed She was incapacitated for one week Difficulty in walking due to diffuse pain and stiffness progressed within the next two years so that she was able to perform only light housework

In November 1935 (in the course of a systematic study of patients with nephrolithiasis) a sample of her blood was submitted to us by Dr S A Beisler Analysis revealed hypercalcemia, hypophosphatemia and increased serum phosphatase activity (table 2) Through the cooperation of Dr C I Buttrick, the patient was admitted to the medical service of the Presbyterian Hospital in January 1936, with the provisional diagnosis of hyperparathyroidism Her chief complaints on admission were difficulty in walking, fatiguability and pain, chiefly in the hips and knees There had been no loss of weight or fractures

The patient was found to be obese (74 kg), pale and chronically ill in appearance There was a definite rounded, non-tender dorsal kyphosis The proximal half of the right tibia was markedly expanded and slightly tender There were no

TABLE II

Serum Calcium, Inorganic Phosphorus, Phosphatase Activity and Non-Protein Nitrogen Before and After Operation in Three Cases of Hyperparathyroidism Simulating or Associated with Paget's Disease

Case	Date	Serum			
		Calcium (mg %)	Inorg P (mg %)	Phosphatase (Bodansky units/100 c c)	Non-protein N (mg %)
A G	11-18-35	12.3	1.9	25.3	36
	12- 2-35	13.4	1.6	26.5	36
	1-16-36	12.6	1.4	20.1	29
	1-28-36	Operation Parathyroid tumor removed			
	1-29-36	10.3	1.4	20.8	34
	1-30-36	8.8	1.7	18.7	36
	2- 3-36	8.6	2.1	23.1	29
	2-11-36	8.1	2.6	24.8	34
	2-21-36	9.6	3.2	17.6	35
	1-19-37	9.9	2.6	13.1	37
	6-23-37	10.5	2.2	12.4	29
M B	12-29-34	14.0	3.0	—	—
	1- 9-35	14.5	3.0	—	—
	7- 6-36	13.7	1.8	2.9	—
	6-17-37	12.6	2.1	3.0	33
	7- 2-37	12.8	1.9	2.7	26
	7- 9-37	Operation Parathyroid tumor removed			
	7-10-37	10.4	2.0	2.7	—
	7-12-37	9.0	2.8	2.2	30
	7-14-37	10.3	2.4	3.1	—
	7-19-37	9.5	2.7	3.3	29
L L	9- 8-30	10.9	—	—	—
	10- 1-35	12.9	1.9	31.4	29
	3-24-36	12.7	1.8	32.6	29
	7-14-36	11.8	2.3	35.2	29
	7-24-36	12.0	2.5	35.5	27
	10- 6-36	11.6	2.8	28.5	29
	10- 7-36	Operation Parathyroid tumor removed			
	10- 9-36	9.5	2.9	26.5	30
	10-13-36	9.6	3.5	34.6	—
	11- 6-36	10.8	3.0	31.3	—
	12- 4-36	11.0	3.1	32.8	—
	1-19-37	10.5	2.7	31.3	28
	4-14-37	10.6	2.8	29.3	32
	4- 6-38	10.7	2.5	30.3	26

other significant findings on physical examination. The right kidney could not be palpated satisfactorily. No palpable tumor was present in the neck.

The urine contained a trace of albumin and occasional pus cells but no casts or Bence Jones protein. Phenolsulphonphthalein excretion was 35 per cent in two hours. There was no nitrogen retention. The erythrocyte and leukocyte counts and the hemoglobin content of the blood were within normal limits. Repeated analyses of the blood showed consistent hypercalcemia, hypophosphatemia and increased phosphatase activity (table 2). Roentgenograms revealed a moderate generalized decalcification of the skeleton with typical blurring of the finer bone architecture. There was a large cyst in the proximal portion of the right tibia (figure 2) and a small cystic area in the region of the medial malleolus on that side. The left side of the pelvis presented Paget-like sclerosis and coarse trabeculations, as described in 1932. These changes were now more extensive and were associated

with obvious cystic involvement (figure 1b) (On reviewing the 1932 films, cysts were recognized in the left innominate and pubic bones) There was no mottling of the skull but two small cysts were present in the occipital region

The calcium excretion on a low calcium diet was studied, the intake being determined by analysis of food aliquots The patient was found to be in negative calcium balance After a preliminary period of six days, the total excretion of calcium per 24 hours (mean of 2 three-day periods) was 0.468 gram on an intake of 0.215 gram per day Seventy-four per cent of the total calcium excreted was in the urine (table 3)

TABLE III

Calcium Balance Studies in Three Cases of Hyperparathyroidism Simulating or Associated with Paget's Disease
(Results expressed in grams per 24 hours, the mean of 3 day periods)

Subject	Period	Ca Intake	Ca Output			Balance	%	Ca in Urine
			Urine	Stool	Total			Total Ca Output
A G	I	215	349	090	439	- 224		79.5
	II	215	343	154	497	- 282		69.0
M B	I	126	126	181	307	- 181		41.0
	II	126	096	354	450	- 324		27.1
L L	I	096	432	126	558	- 462		77.4
	II	094	423	096	519	- 425		81.4

Exploration for parathyroid tumor was performed (W B P) on January 28, 1936 Posterior to the lower pole of the right lobe of the thyroid gland, at about the level of the clavicle, an ovoid, slightly lobulated tumor measuring 4.0 by 2.5 by 1.0 cm was found Three normal parathyroid glands were identified in their usual locations and were not disturbed Histologic study showed the tumor to be an adenoma of the parathyroid gland composed of a solid mass of polygonal cells which were considered to be transitional between the water-clear and chief-cell types

Her postoperative course was uneventful The serum calcium fell rapidly (table 2) and on the second day she complained of mild paresthesias of the extremities which were readily relieved by administration of calcium salts No manifest tetany developed She was discharged February 16, 1936

Two months after operation she was able to resume housework, had gained weight and strength but still complained of some pain in the right knee One year after operation she was in excellent condition and very active

The serum calcium and inorganic phosphorus returned to normal levels within three weeks after operation and have remained normal (table 2) The non-protein nitrogen content of the blood showed no upward trend after operation The phosphatase activity of the serum was not immediately affected by ablation of the parathyroid tumor but began to decline after some months, reaching a level of 124 Bodansky units per 100 cc serum after 17 months, as compared with pre-operative levels of more than 20 Bodansky units The decrease in serum phosphatase activity in this instance was slower than in most cases, but comparable to that observed by us in one patient with proved hyperparathyroidism⁸

Roentgen-rays taken five months after operation showed only slight recalcification At the end of one year, however, there was a definite general increase in bone density, much of the "ground-glass" appearance having disappeared The cystic areas of the left side of the pelvis had become largely sclerosed, with striking diffuse increase of density but without bundling of the trabeculae (figure 1c) The small

cysts in the occipital region of the skull were partially sclerotic Early but definite sclerosis of the large cyst of the right tibia had developed

Case 2 M B, a Syrian woman, aged 54, unmarried, was admitted to the Presbyterian Hospital on June 14, 1937, with the diagnosis of hyperparathyroidism Until 1924 she was well, apparently, and working regularly In February 1924, she fell, fractured the left femur and was hospitalized because of delayed union She has been confined to bed ever since

When admitted to a hospital for chronic diseases in 1924, deformities and bony swellings of both legs and of the left humerus were noted There was expansion of the terminal phalanges, with some fixation of the fingers in flexion Roentgen-rays of the bones showed decalcification and she was diagnosed "osteomalacia" Her course during the next 13 years was characterized by the repeated occurrence of pathologic fractures of the legs, arms and ribs, and by the development of extreme deformities, particularly of the legs She complained intermittently of pain over the bones, but this was never a prominent symptom In 1931 and again in 1933, there were two transitory episodes of weakness and incoordination of the right arm and leg associated with partial aphasia, apparently due to cerebral hemorrhage On one of these occasions, unilateral carpal spasm resembling tetany developed, but without response to calcium therapy There was no history of renal colic, polyuria, polydipsia or gastrointestinal symptomatology (except constipation)

Blood studies in 1934 and 1935 (table 2) showed hypercalcemia but the serum inorganic phosphorus appeared to be within normal limits A specimen of blood was submitted to us for examination in July 1936 by Dr D Seegal On that occasion, hypercalcemia and hypophosphatemia were present The serum phosphatase activity, however, was within normal limits (table 2)

When admitted to the Presbyterian Hospital in 1937, the patient presented a striking picture of the extreme deformities seen in advanced hyperparathyroidism The legs were atrophied, shapeless, bizarrely deformed appendages The pelvis was tilted to the left and distorted There were obvious bony deformities of both arms A rounded dorsal kyphosis of the spine was present The sternum was thrust forward due to flattening of the bony thorax in its lateral dimension The skull was enlarged, somewhat resembling Paget's disease The chin rested on the sternum because of shortening of the neck The interosseous muscles of both hands were atrophied with flexion of the distal phalanges but no obvious clubbing of the fingers Pronounced prognathism was present without evidences of bony tumor of the jaws The teeth were decayed, many were missing She was not in pain when she did not move about in bed The bones of the legs were extremely tender to pressure, however, and there was some tenderness over the ribs, spine and arms A nodular mass was palpable in the neck on the left A purulent discharge was draining from the right antrum Resonance at both lung bases was slightly impaired, occasional coarse râles were heard

The blood Wassermann test was negative Blood counts showed no abnormalities The urine was negative except for the intermittent appearance of a few red blood cells The phenolsulphonphthalein excretion was 37 per cent in two hours Hypercalcemia and hypophosphatemia, but normal serum phosphatase activity, were found consistently After a 5-day fore-period, study of the calcium balance on a low calcium intake (ingested calcium being determined by analysis of food aliquots) showed that, unlike our cases of active hyperparathyroidism, the excretion of calcium in the urine was not excessive

Roentgen-rays of the skeleton showed generalized decalcification of extreme degree, particularly in the bones of the legs (figure 3), in which numerous cysts were present Cysts were also found in the deformed and decalcified pelvis, and in the ribs which, like other bones, were the seat of numerous fractures The vertebrae presented a marked "ground-glass" appearance These skeletal changes were re-

garded as typical of advanced hyperparathyroidism. The cranial vault, on the other hand, was definitely thickened and diffusely sclerotic (figure 4). The "cotton-wool" appearance characteristic of Paget's disease was absent, however. There were no renal calculi.

Exploration on July 9, 1937 (W B P) revealed a tumor 3.0 by 1.2 by 0.5 cm inferior to the left lower pole of the thyroid gland, and extending below the manubrium. Following removal of this tumor, the serum calcium fell rapidly (table 2). Tetany did not become manifest. The mass proved to be a parathyroid adenoma composed largely of chief-cells, some transitional to the water-clear type, and many rose-red cells.

Following operation the patient gained weight and strength and now is able to get about in a wheel-chair.

Case 3 L L, a housewife, then aged 48, came to the Presbyterian Hospital in 1930 for treatment of obesity. Physical examination revealed marked antero-lateral bowing of the right tibia, with slight tenderness. She stated that in 1920 she had developed pain in the lower back and right knee, worse on exercise. The pain in the back largely disappeared, but the knee became worse, proving refractory to physiotherapy. Progressive bowing of the right tibia was noted in 1922, with limp and increasing difficulty in gait since 1925. She thought her head had "always" been large and had not noted any recent increase in size of her hats. There was no loss of hearing. There had been no fractures, no renal colic.

Roentgen-rays of the right tibia in 1930 showed marked antero-lateral bowing with thickening of the cortex and coarse, irregular trabeculations. Areas of decreased density were also thought to be present in the mid-third of the shaft. The film was interpreted as either *osteitis fibrosa cystica* or Paget's disease. The serum calcium in 1930 was found to be normal (10.9 mg per cent, table 2). The blood Wassermann test was negative.

In 1931 roentgenograms of the skull disclosed numerous ill-defined rounded shadows of increased density involving most of the calvarium. There was also some thickening of the floor of the anterior fossa. The changes were regarded then (and now) as typical of Paget's disease. In addition, there was in the occipital region an area of osteoporosis circumscripta, a condition commonly associated with Paget's disease. The diagnosis of Paget's disease was made. Because of persistent pain in the right tibia and also because of severe occipital headache, she received radiotherapy to the right tibia and to the skull for relief of pain. The response was unsatisfactory and she dropped out of sight.

In October 1935, in the course of a study of blood changes in *osteoporosis circumscripta*,⁹ this patient was located and serum obtained for analysis. These determinations unexpectedly showed the presence of hypercalcemia and hypophosphatemia, together with the anticipated rise in serum phosphatase activity (table 2), results suggested hyperparathyroidism rather than Paget's disease.⁸ Reexamination of the blood in March 1936 confirmed these findings (table 2). Repeated roentgenologic studies of the entire skeleton, however, failed to disclose any generalized decalcification or cystic changes. The right tibia again presented the diffusely thickened cortex and coarsely striated trabeculae typical of Paget's disease (figure 5), with distinct distal encroachment since 1931. The characteristic "cotton-wool" appearance of the skull did not resemble the fine, grainy mottling usually seen in hyperparathyroidism. The area of *osteoporosis circumscripta* was now almost completely replaced by sclerotic bone (figure 6).

Because of these discrepancies, the patient was admitted to the medical service of the Presbyterian Hospital in July 1936 for further study. Her presenting complaints on this admission were diffuse pains in both knees, hips, arms and the lower back. Walking had become so labored and painful that she was able to negotiate only short distances. The bowing of the right tibia had progressed, causing shorten-

ing of the right leg and tilting of the pelvis. The severe occipital headaches had recurred. She complained of weakness and fatiguability. There was no interval history of fractures, renal colic, polyuria, polydipsia, gastrointestinal upsets or increase in the size of the head.

Physical examination showed an obese, phlegmatic housewife of 54 years, not in acute pain so long as she remained in bed. The occipito-frontal circumference of the head was 60.5 cm, with questionable parietal bossing. Moderate mid- and upper dorsal kyphosis was present, without tenderness. There was increased antero-lateral bowing of the right tibia (figure 5), which was definitely tender. Other deformities, including clubbing of the fingers, were absent. Except for obesity (205 pounds), examination otherwise was negative. No mass could be palpated in the neck.

Blood counts and urine analysis showed no abnormalities. Hypercalcemia, hypophosphatemia and increased serum phosphatase activity were found consistently on repeated examinations (table 2). The patient was found to be in marked negative calcium balance due to excessive loss of calcium in the urine. After a preliminary period of eight days, the total excretion of calcium per 24 hours (mean of 2 three-day periods) was 539 gram on an intake of 0.095 gram of calcium per day (determined by analysis of food aliquots). Of the total calcium excreted, a mean of 79.4 per cent was in the urine. These results, typical of hyperparathyroidism, are inconsistent with the normal calcium balances found in uncomplicated Paget's disease¹⁰ (see figure 3).

Exploration for parathyroid tumor was performed (W.B.P.) on October 7, 1936. The inferior parathyroid glands on both sides were found slightly enlarged but were not disturbed. At the site of the left superior parathyroid gland, a tumor 2.5 by 1.5 by 1.0 cm. was found and removed. Histologic section disclosed a very vascular parathyroid adenoma composed chiefly of water-clear cells with small, irregular scatterings of "rose red" cells, scarcely any oxyphile cells. Along the margin of the capsule, a remnant of apparently normal parathyroid gland could be seen.

The postoperative course was uneventful. Associated with a fall in serum calcium to normal levels (but not below), the patient complained on the second postoperative day of tingling and numbness of the fingers and of some rigidity of the facial musculature. These symptoms responded readily to calcium administration. She was discharged October 16, 1936.

The patient improved in some respects after operation but the general result after eight months is unsatisfactory. She gained strength and some weight. The headaches disappeared. The pain in the arms vanished but recurred subsequently. The pains in both knees, hips and back are unimproved. These are clearly related to increased activities and are the result of faulty weight distribution due to flat feet and the persisting extreme deformity of the right tibia. Orthopedic measures have not helped. Osteotomy is contemplated.

Roentgen-rays three months after operation showed no change. The calcium and inorganic phosphorus contents of the serum have remained normal (table 2). The postoperative phosphatase activity of the serum, which is being followed with great interest, showed no definite decline six months after removal of the parathyroid tumor (table 2). Our typical cases of hyperparathyroidism exhibited some decrease in serum phosphatase activity within this period though they did not return to normal levels until after the lapse of at least a year.

Discussion Case 1, A. G. The clinical, metabolic and many of the roentgenologic findings in this patient were characteristic of hyperparathyroidism. This diagnosis was established by demonstrating the presence of a typical parathyroid adenoma and by the characteristic postoperative

changes following removal of that tumor. The only atypical finding was the roentgen-ray demonstration of a condensation of bone, simulating Paget's disease, in the pelvis, associated with decalcification and cystic changes in the pelvis and elsewhere.



FIG 1 Case A G (a) Pelvis, 1932, showing area of sclerosis with coarse trabeculations (simulating Paget's disease) in the left ilium, and cystic changes in the pubic bone and ischium (b) Pelvis in 1935, showing more diffuse sclerosis with coarsely striated bone (c) Pelvis in 1937, showing postoperative condensation of bone, indistinguishable from that seen pre-operatively

Parts b and c of Figure 1 continued on pages 22 and 23

It is interesting to note that the sclerotic area present in the pelvis in 1932 (figure 1a) and in 1935 (figure 1b) is indistinguishable in character from the more extensive recalcification of the pelvis observed in postoperative films, and also from the postoperative appearance of recalcifying pelvic bones in some of our other typical cases of hyperparathyroidism. This resemblance suggests the possibility that the sclerosis of bone present in 1932



was not due to Paget's disease but to recalcification associated with an earlier, spontaneous remission of hyperparathyroidism—a transitory remission which preceded the exacerbation precipitating the symptoms that brought this patient to the hospital

It is well known that patients with hyperparathyroidism may show distinct remissions and exacerbations in the course of the disease. In fact, complete spontaneous recovery has been described^{1, 5, 10, 11}. In such cases, recalcification following spontaneous recovery from hyperparathyroidism resulted in skeletal changes indistinguishable from those seen after surgical ablation of parathyroid tumors.

Ordinarily, the roentgenographic appearance of recalcifying bone, whether postoperative or spontaneous, could hardly be confused with Paget's disease. Cystic areas, particularly in the extremities, usually fill in to form a solid, structureless mass of sclerotic bone which shows none of the architecture characteristic of most Paget lesions. In the pelvis, however, as is evident from published cases and from our own postoperative observations, the resulting sclerosis may be more diffuse and the end-result may be difficult to distinguish from the sclerotic phase of Paget's disease^{11, 12}. Such changes have often been referred to in the literature as "pagetoid"¹¹. To call them Paget's disease,¹³ however, would seem at this time to be unjustified^{1a, 7, 11, 12, 14, 15}.



In summary then, case A G appears to be an instance of hyperparathyroidism simulating certain roentgenologic aspects of Paget's disease. The atypical, localized bone condensation simulating Paget's disease may well be the result of an earlier transitory, spontaneous remission in the course of hyperparathyroidism.

Case 2, M B Deformities typical of advanced hyperparathyroidism were associated in this patient with profound skeletal decalcification and numerous bone cysts, and with hypercalcemia and hypophosphatemia. The diagnosis of hyperparathyroidism was established by demonstrating the presence of a parathyroid adenoma. An apparently discrepant finding, however, was the enlargement of the skull with definite thickening and sclerosis of the cranial tables, superficially resembling that seen in some cases of Paget's disease.

The absence of "cotton-wool" lesions in the skull and of any increase in serum phosphatase activity⁴ argue against the presence of Paget's disease in this patient. Expansion and sclerosis of the cranium have been described in many published cases of proved hyperparathyroidism (*vide infra*). We have ourselves seen similar skull changes develop postoperatively in healing

* The phosphatase activity of the serum is definitely increased in hyperparathyroidism too, ordinarily,⁸ at least in cases with marked skeletal changes. It is possible that in this patient, destruction of bone was so extensive and of such long standing that bone repair was virtually at a stand-still. The atypical calcium balance is consistent with this possibility.

hyperparathyroidism Such sclerotic transformation of the skull may well be due to recalcification occurring with remission in the course of hyperparathyroidism In support of this interpretation, the calcium balance results were consistent with reduced or insignificant parathyroid over-activity at the time our studies were made



FIG 2 Case A G, right tibia, showing decalcification and large cyst of the proximal half of the tibia, typical of hyperparathyroidism

We regard case M B, then, as an instance of advanced generalized *osteitis fibrosa cystica* with only moderately over-active parathyroid function when operated upon, and presenting spontaneous recalcification of the skull simulating Paget's disease superficially

Case 3, L L In this instance, the roentgenograms were typical of *osteitis deformans*, the clinical symptoms and signs suggested Paget's disease but were not incompatible with hyperparathyroidism, and the blood analyses and markedly negative calcium balance due to loss of calcium in the



FIG 3 Case M B, right femur and proximal third of tibia The deformities, extreme decalcification and multiple cyst formation are typical of advanced hyperparathyroidism

urine clearly indicated parathyroid over-activity The diagnosis of hyperparathyroidism was established by demonstrating the presence of a parathyroid tumor, such tumors not being found in patients with unequivocal and uncomplicated Paget's disease¹⁰

Nevertheless, certain aspects of this case seem to us to be incompatible with the diagnosis of hyperparathyroidism We could not find cases of hyperparathyroidism in the literature, nor have we seen any ourselves, with pre- or postoperative bone lesions comparable to those present in the right tibia of this patient (figure 5) The roentgenographic appearance of the tibia satisfies all the currently accepted criteria of typical *osteitis deformans*, and is indistinguishable from that of many patients in the large series of Paget's disease which we have had the opportunity to study⁷ The appear-

ance of the skull, too, is characteristic of Paget's disease, though the skull mottling of hyperparathyroidism may be so coarse as to simulate this aspect of Paget's disease, particularly in some cases after operation. The presence of *osteoporosis circumscripta* of the skull (not to be confused with bone cysts occasionally found in the skull in hyperparathyroidism) provides further evidence for the interpretation of Paget's disease.¹⁷



FIG 4 Case M B, skull showing expansion and diffuse sclerosis of the cranial tables

The postoperative course of this patient, unsatisfactory in many respects, likewise suggests the possibility of a bone lesion not due to hyperparathyroidism. And while the period of observation is yet too short, the persistently high postoperative level of serum phosphatase activity, despite the normal calcium and inorganic phosphorus content of the serum, is quite consistent with Paget's disease but contrary to what we have found in hyperparathyroidism.

The interpretation of this case which seems to us to do least violence to what is known about both diseases is that this is an instance of hyperparathyroidism associated with Paget's disease. Whether or not the presence of Paget's disease in this instance precipitated the development of hyperparathyroidism (or vice versa), is a matter of speculation. These possibilities cannot be ruled out. But in view of the evidence for the view that hyperparathyroidism and Paget's disease are discrete and unrelated entities, this seems unlikely.

The fortuitous co-existence of Paget's disease and hyperparathyroidism is not as improbable a coincidence as may appear. As is becoming in-

creasingly apparent, Paget's disease, far from being a rarity, is not uncommon, particularly at this patient's age period.⁷ Moreover, a critical examination of the literature shows that the number of cases which can

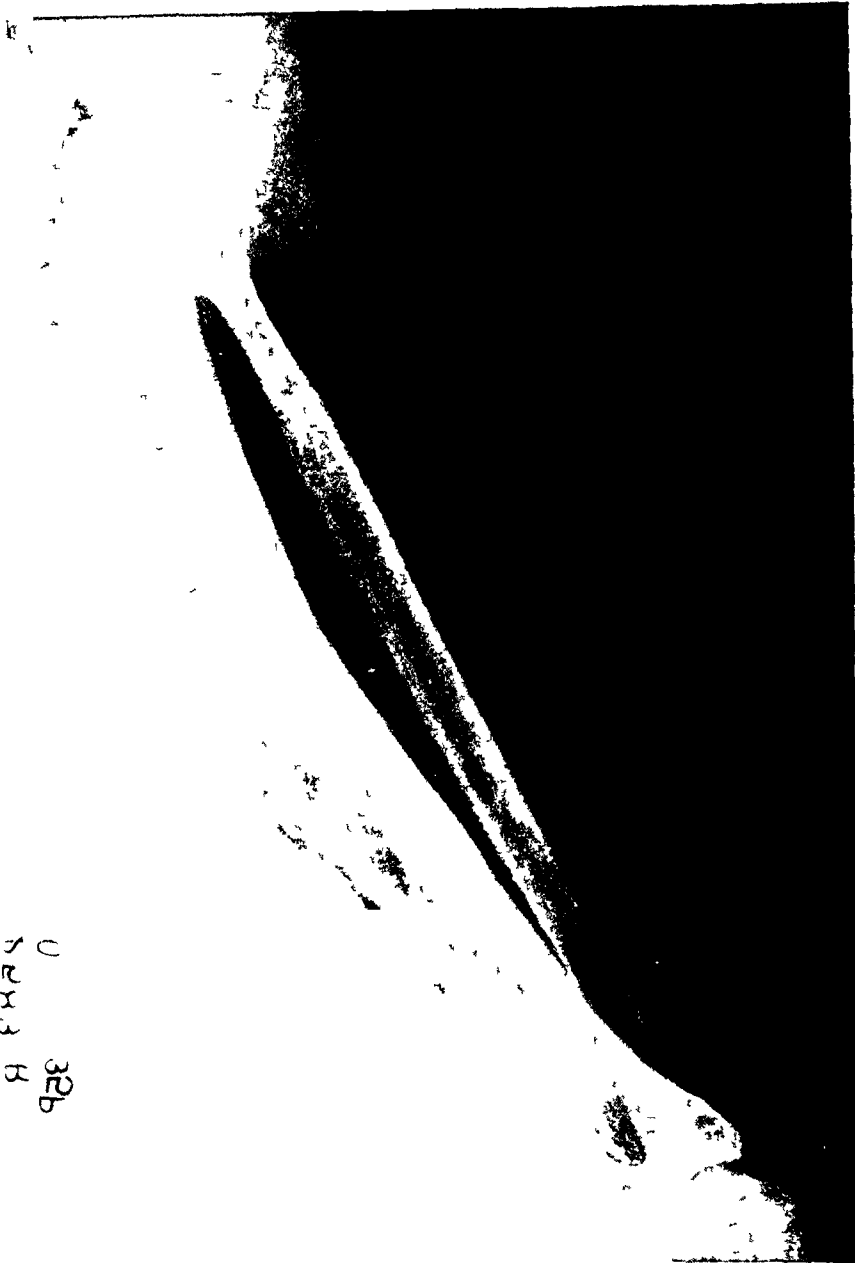


FIG 5 Case L L, right tibia, showing expansion with antero-lateral bowing, marked cortical thickening and coarse trabeculations consistent with Paget's disease

really be regarded as presenting both hyperparathyroidism and Paget's disease is very small

Cases in the Literature The literature contains a number of cases presenting aspects suggestive of both hyperparathyroidism and Paget's disease. In many instances, however, particularly in the older literature, the mottling

of the skull now known to be typical of hyperparathyroidism was called "pagetoid" or confused with the "cotton-wool" appearance of Paget's disease. The skull changes in hyperparathyroidism may include definite expansion of the tables and when recalcification takes place, considerable sclerosis, either diffusely uniform or localized to one or more areas. Thickening of the skull, of marked degree in several instance,^{18, 19, and others} was



FIG 6 Case L L The skull presents the typical "cotton-wool" appearance of Paget's disease

described in 18 proved cases of hyperparathyroidism in the literature. The pelvis was the site of sclerotic bone lesions in several proved cases of hyperparathyroidism,^{14, 20, 21, and others} as pointed out in connection with Case 1, A G. Sclerotic areas have been found, further, in the vertebrae,^{22, 23, 24, and others} possibly due to compression fractures, and associated with healed fractures of the ribs. The bones of the extremities are more likely to show localized condensations of bone, obviously sclerosed cysts, but diffuse sclerosis, cortical thickening and coarsely striated trabeculae (accompanying severe deformities) have been described^{25, 26, 11}

These areas of sclerosis did not resemble Paget's disease, for the most part, and were regarded usually as atypical manifestations of hyperparathyroidism. The observations of Kienbock and Markovits,¹¹ of Mandl¹⁵ and others suggest that the condensation of bone in many such instances is due to spontaneous recalcification occurring in the course of hyperparathyroidism.

Some cases interpreted as both hyperparathyroidism and Paget's disease would appear to be Paget's disease with cyst-like areas due to fatty degeneration of the bone marrow or to accumulations of osteoid tissue¹⁶, or Paget's disease with secondary decalcification such as is seen after prolonged immobilization. Other cases in this category are reported too briefly for evaluation.

There remain a few instances, such as Case 3, L. L., of this report, in which both hyperparathyroidism and Paget's disease appeared to be present. The coexistence of both diseases in these instances would appear to be fortuitous. An alternative explanation has been offered by Albright, Aub and Bauer.¹⁴ If the unknown factor stimulating osteoclastic activity in Paget's disease is present in a patient in subthreshold degree, superimposed hyperparathyroidism, with its generalized stimulus to osteoclastic activity, may make the underlying disease become manifest.

Whatever the explanation for these cases, we feel justified in concluding that they do not seriously jeopardize the prevailing view that hyperparathyroidism and Paget's disease are distinct and unrelated entities. They serve, however, to emphasize two practical points: 1. Cases of hyperparathyroidism may present isolated areas of bone sclerosis, 2, appropriate chemical studies should be made even in cases of apparently obvious Paget's disease to exclude the possibility of hyperparathyroidism.

SUMMARY

1. Three proved cases of hyperparathyroidism are described, two presenting sclerotic lesions simulating Paget's disease, of the pelvis in one instance and of the skull in the other, and the third case apparently associated with Paget's disease of the tibia and skull.

2. A review of the literature shows that isolated areas of sclerotic bone may develop in hyperparathyroidism, particularly in the skull and pelvis. Most such areas resemble recalcification observed postoperatively and appear to be the result of spontaneous recalcification of the bones occurring in remission. Occasionally, the sclerotic bone lesions may simulate Paget's disease.

3. Cases of proved hyperparathyroidism associated with what appears to be typical Paget bone involvement have been described, but are very few in number. These few cases are thought to be not incompatible with the view that hyperparathyroidism and Paget's disease are distinct and unrelated entities.

BIBLIOGRAPHY

- 1 a MICHALLIS, L Ostitis deformans (Paget) und Ostitis fibrosa (von Recklinghausen), *Ergebn d Chir u Orthopadie*, 1933, xxvi, 381
- b HUNTER, D, and TURNBULL, H M Hyperparathyroidism Generalized osteitis fibrosa, *Brit Jr Surg*, 1931, xix, 203
- c BAUER, W Hyperparathyroidism A distinct disease entity, *Jr Bone and Joint Surg*, 1933, xv, 135
- d AIBRIGHT, F, AUB, J C, and BAUER, W Hyperparathyroidism, *Jr Am Med Assoc*, 1934, cii, 1276
- e GUTMAN, A B, SWINSON, P C, and PARSONS, W B The differential diagnosis of hyperparathyroidism, *Jr Am Med Assoc*, 1934, ciii, 87
- 2 MANDL, F Klinisches und Experimentelles zur Frage der lokalisierten und generalisierten Ostitis fibrosa, *Arch f klin Chir*, 1926, cxliii, 1, 245
- 3 CHRISTELLER, E Referat über die Osteodystrophia fibrosa, *Verhandl d deutsch path Gesellsch*, 1926, xxi, 7
- 4 WILlich, T Spontane Ausheilungsvorgänge bei generalisierter Osteodystrophia fibrosa, *Beitr z klin Chir*, 1929, cxlvi, 103
- 5 MEYER-BORSTEL, H Über die Stellung der Recklinghausenschen zur Pagetschen Knochenkrankung, *Fortschr a d Geb d Roentgenstrahlen*, 1930, xlii, 493
- 6 GUTMAN, A B The parathyroid glands, *Nelson Loose-Leaf Medicine*, 1935 revision, Thomas Nelson & Sons, New York
- 7 GUTMAN, A B, and KASABACH, H Paget's disease (osteitis deformans) Analysis of 116 cases, *Am Jr Med Sci*, 1936, cxcii, 361
- 8 GUTMAN, A B, TYSON, T L, and GUTMAN, E B Serum calcium, inorganic phosphorus and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of the bones, *Arch Int Med*, 1936, lvii, 379
- 9 GUTMAN, A B, GUTMAN, E B, and KASABACH, H H Serum phosphatase activity in seventeen cases of osteoporosis circumscripta of the skull, *Proc Soc Exper Biol and Med*, 1935, xxxiii, 295
- 10 LINDEN, O Case of osteitis fibrosa generalisata with well-marked tendency to spontaneous cure, *Acta radiol*, 1934, xv, 202
- 11 KIENBOCK, R, and MARKOVITS, E Ein Fall von Ostitis fibrosa cystica generalisata, *Fortschr a d Geb d Roentgenstrahlen*, 1930, xli, 904
- 12 ASK-UPMARK, E Further observations on osteitis fibrosa generalisata, *Acta chir Scandinav*, 1931, lxxviii, 551
- 13 KIENBOCK, R Über die Pagetsche Knochenkrankheit und Epithelkörperchentumoren, *Beitr z klin Chir*, 1934, clx, 597
- 14 LILVRE, J A L'osteose parathyroïdienne et les osteopathies chroniques, *Masson et Cie*, Paris, 1932
- 15 MANDL, F Der Kalkstoffwechsel und seine Beziehungen zur Chirurgie der Epithelkörperchen, *Beitr z klin Chir*, 1935, clxii, 643
- 16 SCHMORL, G Über Ostitis deformans Paget, *Virchow's Arch f path Anat*, 1932, cclxxxiii, 694
- 17 KASABACH, H H, and GUTMAN, A B Osteoporosis circumscripta of the skull and Paget's disease Fifteen new cases and a review of the literature, *Am Jr Roentgenol*, 1937, xxxvii, 577
- 18 SCHMORL, G Demonstrationen, *Verhandl d deutsch path Gesellsch*, 1913, xvi, 352
- 19 PENECKE, R Ueber zwei Fälle von Ostitis fibrosa Recklinghausen mit Epithelkörperchentumoren, *Verhandl d deutsch path Gesellsch*, 1926, xxi, 97
- 20 THOMASON, G, and SMITH, L Hyperparathyroidism, *West Jr Surg*, 1933, xli, 78
- 21 RIVEN, S S, and MASON, M F Adenoma of the parathyroid gland, with hyperparathyroidism, *ANN INT MED*, 1936, ix, 1578

- 22 HANKE, H Pathologische und theoretische Untersuchungen uber Osteodystrophia fibrosa (von Recklinghausen) und ihre Beziehung zu Epithelkorperchentumor, Arch f klin Chir, 1932, cclvii, 366
- 23 PINELLI, L Descrizione d'un caso presentante processi di osteodistrofia deformante del cranio e della colonna vertebrale e contemporane alter alterazioni di osteite fibrosa cistica degli arti, Annali di radio e fisica med, 1934, vii, 270
- 24 LAHEY, F H, and HARGART, G E Hyperparathyroidism, Surg, Gynec and Obst, 1935, lx, 1033
- 25 HOFFHEINZ Ueber Vergrosserungen der Epithelkorperchen bei Ostitis fibrosa und verwandten Krankheitsbildern, Virchow's Arch f path Anat, 1925, cclvi, 705
- 26 SAINTON, P, and MILLOT, J L Les lesions osseuses et parathyroidiennes dans la maladie de Recklinghausen, Ann d'anat Path, 1931, viii, 70

THE OXYGEN THERAPY OF PNEUMONIA

(FIVE YEARS' EXPERIENCE AT THE U S MARINE HOSPITAL,
NORFOLK, VIRGINIA) '

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THE use of oxygen as a therapeutic agent in pneumonia had its origin in the work of Haldane ² and Meltzer ⁵ Among the earlier methods of administration was the face mask of Haldane and the hollow tongue compressor of Meltzer Later, oxygen chambers were constructed at the Rockefeller Institute by Stadie and Binger, by Barach at the Presbyterian Hospital, New York, and by Boothby at the Mayo Clinic It was not, however, until the introduction of bed tents, originally designed by Hill and modified by Roth, Binger, Barach and others, that it was possible to apply oxygen therapy to large groups of patients

The physiological basis of oxygen therapy is well understood The effect of anoxemia has been studied at high altitudes and experimentally in animals, in closed chambers from which oxygen has been partially exhausted The symptoms of fatigue, cyanosis, nausea, delirium, and collapse have been observed in both instances Stadie ⁸ showed that there was a decreased oxygen saturation of the arterial blood in cyanosed pneumonia patients, and that the degree of under-saturation in these patients approached that found in severe mountain sickness Meakins ⁴ demonstrated that the cyanosis could be relieved, and the oxygen content of arterial blood returned to an approximately normal level by the inhalation of an oxygen mixture of sufficient concentration In spite of these considerations, there is still considerable skepticism among clinicians as to the actual therapeutic value of oxygen in pneumonia This skepticism is the result of the misuse or abuse of oxygen therapy To a large extent, oxygen has been reserved for the seriously ill or almost moribund patients The death rate among this group has naturally been very high There are, as far as we know, no statistical data bearing on the routine adequate use of oxygen in pneumonia, nor a comparison of such a group with a control group of similar cases not so treated It is our purpose, therefore, in this discussion, to offer certain figures bearing on the result of the early and adequate use of oxygen in pneumonia, and to present for comparison a similar group of cases in which oxygen was not used A little over five years ago, oxygen therapy was first begun as a routine measure in the treatment of pneumonia patients at the U S Marine Hospital, Norfolk, Virginia, at the instigation of Surgeon S L Christian, Medical Officer in Charge, and carried out under the supervision of Surgeon W L Smith, United States Public Health Service

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Since then it has been the rule to start oxygen on all cases of pneumonia as soon as the diagnosis is established, and to continue its use throughout the course of the disease, at a concentration of between 40 per cent and 60 per cent. Full credit should be given to the above mentioned officers for the adoption of this program in this hospital. So strong was their faith in the procedure that they seem to have converted the entire medical and nursing staff to their views on the subject.

Technic The patient is made to understand that he will have to live beneath the tent during the entire duration of his disease, and that increased oxygen concentration is considered an important factor in his recovery. The oxygen tent is then placed over the patient, the flaps properly tucked under the mattress and the bed covers, and every effort made to prevent any possible leakage of air. It has been found by experience that with a good tight tent, 6 liters of oxygen per minute must be allowed to enter the tent, in order to maintain an oxygen content of 40 per cent to 60 per cent. This is thought by Barach to be the optimum concentration in the treatment of pneumonia. Frequent gasometric tests are necessary to ascertain the actual oxygen percentage. If the concentration is found below the optimal level, it is usually shown that a leaky tent needs adjustment.

Occasionally a greater supply of oxygen may be temporarily required. The proper level of temperature and moisture within the tent are automatically controlled by electric blowers that force circulation through a cooling dryer device containing cracked ice. Carbon dioxide is absorbed by its passage through a soda lime container.

The relatively high cost of continued oxygen therapy has deterred its more widespread adoption in the treatment of pneumonia. If, however, it can be demonstrated that its adequate use will result in the saving of lives, the cost factor becomes much less important.*

Statistics In cooperation with a state wide study of pneumonia statistics, it became necessary to review the records of all pneumonia patients treated in this hospital for the last 10 years. This afforded an excellent opportunity for the evaluation of oxygen therapy in pneumonia. During the first four years of this period, oxygen was not employed. Its use was started in the spring of 1931. During the last five years, it has been a routine therapeutic measure, as outlined above. The figures for 1931, although favorable to oxygen therapy, were purposely omitted from the record, since the objection might be raised against them that the seasonal distribution influenced the good results. The total mortality of the 26 pneumonia patients during the year was approximately 21 per cent. The mortality without oxygen was 33.3 per cent, and that with oxygen 16.6 per cent.

* The cost of operating such an outfit on the above technic has been estimated at approximately \$5.00 a day. A tank of 220 cu. ft. of commercial oxygen at \$2.00 will last about 18 hours. Five pounds of soda lime at \$2.50 must be renewed every 24 to 36 hours. This frequent changing of soda lime renders the gasometric testing of carbon dioxide unnecessary.

The following tables show the comparative figures for the other years of the decade under study

TABLE I
(A) Pneumonia Treated Without Oxygen *

	1927	1928	1929	1930	Total
Lobar pneumonia	13	11	12	13	49
Deaths	4	3	6	3	16
Percentage	30.8	27.3	50.0	23.1	32.65
Bronchopneumonia	10	5	11	12	38
Deaths	2	1	3	5	11
Percentage	20.0	20.0	27.3	41.7	28.95

(B) Pneumonia Treated With Oxygen *

	1932	1933	1934	1935	1936	Total
Lobar pneumonia	9	11	9	16	19	64
Deaths	1	3	1	4	3	12
Percentage	11.1	27.3	11.1	25.0	15.8	18.75
Bronchopneumonia	5	4	9	15	9	42
Deaths	1	1	2	1	2	7
Percentage	20.0	25.0	22.2	6.7	22.2	16.7

* All cases except terminal pneumonia

TABLE II
Percentage Based on All Cases, Including Terminal Pneumonia

(A) Without oxygen 1927-1931	Mortality
Lobar pneumonia	42.1
Bronchopneumonia	34.1
(B) With oxygen 1932-1937	
Lobar pneumonia	31.9
Bronchopneumonia	29.0

TABLE III
Age Distribution

Age	(A) Without Oxygen (1927-1931)		(B) With Oxygen (1932-1937)	
	Cases	Deaths	Cases	Deaths
10-20	5	1	11	0
20-30	16	5	29	5
30-40	31	7	28	4
40-50	23	7	19	5
50-60	9	6	14	2
60-70	3	1	1	0
70-80	0	0	3	2
80-90	0	0	1	1

Experience with oxygen in two general hospitals in Norfolk, namely, Norfolk General Hospital and St Vincent's Hospital, forms an interesting contrast with that embodied in the figures quoted above

Table 6 includes all cases in these two hospitals on which accurate records of the amount of oxygen administered in the treatment of pneumonia are available

TABLE IV
Racial Distribution

	(A) Without Oxygen (1927-1931)						
	White		Negro		Total White	Total Negro	Grand Total
	Lobar Pneumonia	Broncho-pneumonia	Lobar Pneumonia	Broncho-pneumonia			
Cases	32	26	17	12	58	29	87
Deaths	10	8	6	3	18	9	27
Percentage	31.25	30.6	35.3	25	31	31	31
	(B) With Oxygen (1932-1937)						
	White		Negro		Total White	Total Negro	Grand Total
	Lobar Pneumonia	Broncho-pneumonia	Lobar Pneumonia	Broncho-pneumonia			
Cases	39	28	26	13	67	39	106
Deaths	8	7	4	0	15	4	19
Percentage	20.5	25	15.4	0	22.4	10.25	17.9

TABLE V
Average Duration of Disease Before Admission

(A) Without Oxygen (1927-1931)		(B) With Oxygen (1932-1937)	
Lobar pneumonia	3.5 days	Lobar pneumonia	3.2 days
Bronchopneumonia	4.2 days	Bronchopneumonia	4.1 days

TABLE VI
All Pneumonias 1932-1937

Cases	Deaths	Recoveries	Percentage of Deaths
626	231	395	35.3
Cases Receiving Oxygen			
65	48	17	73.8
Oxygen—70 Hours or More			
9	3	6	33.3
Oxygen—30 Hours or Less			
37	32	5	86.5
Average Duration of Oxygen Therapy 29.6 hours			

It is evident, from the figures in table 6, that oxygen therapy was reserved for the most desperate cases and was often a farewell gesture rather than a well conceived therapeutic effort. In only a small number of cases was oxygen given over a long enough time to be effective. It is to be noted that even in this group of severe cases, the death rate on the number receiving what might be termed adequate oxygen treatment (70 hours or more) was slightly less than the average death rate on all cases of pneumonia in these two hospitals. The report of Painton and Ulrich⁶ conforms closely to these figures. Of 149 patients receiving oxygen therapy on their service, 60 per cent died. It can readily be understood that with such experiences the average physician might assume that the use of oxygen in pneumonia is valueless.

SOCIAL AND ECONOMIC STATUS

Practically all of these patients treated at the U. S. Marine Hospital in both series came from the laboring classes. Most of them were merchant seamen, coast guardsmen, and civilian conservation corps boys. All but four were male. In nearly every case the clinical diagnosis was confirmed by roentgen-ray.

From the above data it is evident that the classes of patients treated with and without oxygen were similar in every respect. They received the same type of nursing and medical care in the same hospital with only one striking exception, namely oxygen therapy. A glance at the tables will suffice to show that there was an appreciable decline in mortality following the institution of this therapeutic measure. Serum therapy did not enter into the picture, since only one patient received this treatment. He was a Type I pneumonia patient in the 1936 group, who was given 110,000 units of Felton Type I serum, and recovered.

Comments. It is a fact that anoxemia, a reduction of oxygen in the arterial blood, occurs to some extent in every case of pneumonia. When this is sufficiently marked it will manifest itself by cyanosis. That anoxemia is a harmful condition is at present recognized by all. Barach expresses it well when he sums up its effects as follows: "In summary, it might well be said that the disturbance of the gastrointestinal system is manifested by nausea, vomiting and diarrhea, the respiratory system by increased rate and depth of respiration or by periodic respiration, and later by rapid shallow respiration, the circulatory system by a constant and progressive increase in pulse rate, and in the end by a fall in diastolic pressure and cardiac failure, the central nervous system by headache, visual disturbances, irrational states and delirium, and finally, by coma and death." Hence the appearance of any of these symptoms in pneumonia may be attributable to a certain degree to anoxemia.

In combating anoxemia, by increasing the oxygen of the circulating blood, oxygen therapy acts not only locally in the lungs but throughout the body. Oxygen is a need of all the tissues, and the proper function of all the

organs depends upon its adequate supply through the circulating blood. This is the reason that in order to be most efficacious in pneumonia, oxygen administration must be begun early in proper concentration and continued throughout the course of the disease.

It is our opinion that the prevention of cyanosis rather than the treatment of cyanosis after it has developed is the important objective. A severe degree of anoxemia may lead to irreversible degenerative changes.

Beneficial Effect of Oxygen It has been claimed that the beneficial effects of oxygen in pneumonia are manifested in various ways. These have been listed by different authors as follows:

- (1) A disappearance of cyanosis
- (2) A reduction of the respiratory rate
- (3) A diminution of the heart beats
- (4) A lowering of the body temperature
- (5) A lessening of the harassing cough
- (6) An elevation of the blood pressure
- (7) A prolongation of life allowing more time for the development of the immunization phenomena

In our experience it seems difficult to substantiate all of these claims. An actual lowering of the temperature, pulse, and respiration curve cannot usually be demonstrated on the patient's chart. The course of the disease is not shortened. What has been observed is that the patient becomes quieter, breathes easier, and will often fall into a restful sleep following oxygen inhalation. Cyanosis and delirium are lessened, and the general condition and comfort of the patient seem distinctly improved. It is frequently noted that the patient requests that he be placed under the oxygen tent again, when it has temporarily been removed.

Recent Developments Because of the high cost of soda lime, the discontinuance of its use has recently been advised. Rosenbluth shows that a supply of oxygen, at 6 liters per minute, will permit the carbon dioxide to accumulate only up to 4 per cent within a properly closed tent, if soda lime is not used to absorb it. By increasing the inflow of oxygen to 8 to 10 liters per minute, the carbon dioxide will not rise above 1.5 per cent which is well within the limits of safety. He believes that an atmosphere containing even 2 to 4 per cent of carbon dioxide is not detrimental to the patient. From the above it is evident that the soda lime can be dispensed with and at a little saving. Some of the newer oxygen tents on the market are built upon this principle. There is an additional advantage in the increased oxygen allowance, in that it permits the nurse greater freedom in handling the patient. The avoidance of slight leaks becomes relatively less important.

Henderson³ advocates the addition of carbon dioxide to oxygen (his carbogen) in the treatment of pneumonia. He believes that a concentration of 4.5 to 5 per cent of carbon dioxide is definitely beneficial. He states

"The results reported indicate, and more recent extensive unpublished experience confirms, that inhalation of carbogen (5 per cent carbon dioxide in 95 per cent oxygen) affords the same benefit in overcoming cyanosis as does oxygen and has the additional advantage of inducing also a deeper and often slower rate of breathing." These claims of Henderson have, however, not been confirmed.

The danger of the inhalation of too high a percentage of oxygen upon the parenchyma of the lungs which was formerly so strongly stressed seems, perhaps, to have been exaggerated. Evans and Durshordwe¹ demonstrate that even at nearly a 100 per cent concentration, oxygen does not seem to irritate the pulmonary tissues.

In view of these recent developments, it is proposed to modify the present technic of oxygen tent operation in this hospital. In the future, the oxygen flow will be adjusted at 10 liters per minute, and the soda lime will be discarded. The results of this new phase of oxygen therapy, and whether the present good record can be still further improved, will remain for the future to decide.

CONCLUSION

- (1) In our experience a very definite lowering of mortality in both lobar and bronchial pneumonia has been observed since the institution of routine oxygen therapy at the U S Marine Hospital in Norfolk.
- (2) In order to obtain optimal results in pneumonia, oxygen therapy should be started early and should be continued in adequate concentration throughout the course of the disease.

REFERENCES

- 1 EVANS, J H, and DURSHORDWE, C J Further observation on oxygen therapy in the treatment of pneumonia, *Current Researches in Anesthesia and Analgesia*, 1932, xi, 193
- 2 HALDANE, J S The symptoms, causes and prevention of anoxemia, *Brit Med Jr*, 1919, ii, 65
- 3 HENDERSON, YANDELL Reasons for the use of carbon dioxide with oxygen in the treatment of pneumonia, *New England Jr Med*, 1932, ccvi, 151
- 4 MEAKINS, J C Therapeutic value of oxygen in pulmonary lesions, *Brit Med Jr*, 1920, i, 324
- 5 MELTZER, P J The therapeutic value of oral rhythmic insufflation of oxygen, *Jr Am Med Assoc*, 1917, lxi, 1150
- 6 PAINTON, F J, and ULRICH, H J Lobar pneumonia an analysis of 1298 cases, *ANN INT MED*, 1937, x, 1345
- 7 ROSENBLUTH, M B, and BLOOM, M Oxygen therapy, *Jr Am Med Assoc*, 1932, xcvi, 396
- 8 STADIE, W C The oxygen of the arterial and venous blood in pneumonia and its relation to cyanosis, *Jr Exper Med*, 1919, xxx, 215

SECONDARY AMYLOIDOSIS· RESULTS OF THERAPY WITH DESICCATED WHOLE LIVER POWDER¹

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AMYLOIDOSIS secondary to a chronic infection is a complication of serious prognostic significance. In human beings presenting clinical signs of amyloidosis, the condition usually progresses to a fatal termination because the underlying cause remains active. Very few reported cases of recovery appear in the literature¹⁻¹. The majority of these recover only after an extensive operation which eradicates the primary disease provided the operative procedure is carried out early. This method of treatment can be employed with success only in a limited number of instances. The treatment of secondary amyloidosis in the majority of patients is therefore directed towards mitigating the primary illness through general measures. The results hitherto have been wholly unsatisfactory. Prior to the institution of the therapy which will be described later, all our patients died within two years¹⁴.

Several years ago, we observed clinical evidence of the disappearance of amyloid in human beings even in the presence of active tuberculous sup-puration of bone following the administration of a powdered whole liver preparation. Brief mention of this was made at that time^{8, 15, 16}. However, we have felt the need for further clinical observation and investigation, as well as a more extended experimental study. This caused us to delay the present report. Our original observations have now the support of well controlled laboratory studies. In the meantime, a preliminary report of our early results was made by Whitbeck⁹. It is over eight years now since the institution of this therapy at Neponsit Beach Hospital for Children. Our clinical success with this material which has been substantiated by our ex-perimental work^{15, 16} and confirmed¹² by others, warrants a more detailed presentation of our results.

The diagnosis of amyloidosis was made in each case after a period of observation and study of at least four to six months. All subjects had a primary suppurative disease of long standing and showed classical symptoms of amyloidosis consisting of waxy pallor, loss of weight, emaciation, weak-ness, large abdomen with dilated and tortuous superficial abdominal veins, marked and progressive hepatomegaly and splenomegaly, albuminuria and casts of every description, and positive Congo Red test giving 100 per cent withdrawal of intravenously introduced dye.

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After it was definitely established that amyloidosis was present and after a minimum period of six months had elapsed during which time it was observed that the lardaceous condition was progressing unfavorably, liver therapy was instituted in selected cases. The treatment consisted of the administration of a desiccated powdered whole liver preparation in doses of 4 to 8 grams three times a day*.

It was given in a suitable vehicle such as fruit juices, cereal, milk, jelly or jam. In addition to the liver therapy, the usual general hygienic and medical measures were carried out such as an adequate diet, fresh air, sunlight, heliotherapy, daily salt water baths and dressing, and some form of orthopedic non-surgical immobilization. These latter measures differed in no wise from similar measures employed in each case before liver therapy was instituted.

CASE REPORTS

Case 1 J. G., male white child, 8 years old on admission, entered Neponset Beach Hospital for Children on May 29, 1923. He had tuberculous disease of the second, third and fourth lumbar vertebrae. There were two discharging sinuses, one in the left gluteal region and one in the left iliac region just to the inner side of the left anterior superior spine. By January 16, 1924, the sinuses had closed and were apparently healed, and on March 24, 1924, a plaster jacket was applied. He was allowed out of bed for short periods of time, but on March 20, 1925, the sinuses re-opened and commenced to discharge. The temperature was elevated, reaching 104° F.

The unfavorable condition persisted. The child displayed a poor appetite, lost weight and became increasingly paler. By July 1926, definite amyloidosis may be said to have set in. The liver and spleen were 2.5 and 1.3 cm. respectively below their corresponding costal borders in the mid-clavicular line†. The child's condition declined progressively so that by April 14, 1929 his state was critical. He was very emaciated and pale, and had several attacks of epistaxis, hematemesis and melena. There was generalized anasarca including hydrothorax and ascites. The liver edge was below the crest of the ilium and the spleen was down 11.5 cm. At this time whole powdered liver was given in doses of 4 gm. three times daily and within one month increased to 8 gm. three times daily.

Within six months after the administration of the liver therapy there was striking improvement in the patient's general appearance and in his clinical symptoms. Although the temperature was still moderately elevated, and the sinuses continued to discharge freely, the generalized anasarca had completely disappeared, the superficial abdominal veins were much less prominent and the liver and spleen were 5 cm. and 3 cm. respectively. The subsequent course was favorable. After one year of treatment and in spite of the persistence of signs of activity as evidenced by the presence of fever, discharging sinuses and progressive destruction in the bones seen in the roentgenograms, the liver was 2.5 cm. and the spleen was just palpable. Albuminuria was still marked. Two and one half years of therapy resulted in the

* The whole liver powder is one that must be prepared under certain specific conditions so that in the process of desiccation, the chemically unknown principle is not destroyed or reduced in its potency. Briefly, we would consider a suitable method of preparation one which consists of removing extraneous material from the liver, chopping up the livers and drying them in vacuum. The temperature should not be above 35° F., preferably below this level.

† In succeeding enumerations of the size of the liver and spleen, mention will be made only in terms of centimeters, it being understood that such measurements are made in the mid-clavicular line below their costal margins.

complete recession of the liver and spleen so that they were no longer palpable. At approximately this period the sinuses closed and have remained healed up to the present. To date, after a period of nearly eight years, the child has remained clinically well and is quite active. Congo red test showed 100 per cent withdrawal of the dye in April 1929 and again in July 1931.

Case 2 C I, male white child, 7½ years on September 8, 1924, the date of admission to Neponsit Beach Hospital for Children. About three months prior to admission, there developed pain and swelling of the right knee associated with fever. The condition became progressively worse so that on admission, the child was pale and emaciated and presented a marked fusiform swelling of the right knee with several discharging sinuses.

High temperature with discharging sinuses, loss of weight, increasing anemia and albuminuria continued and by January 1927, the abdomen was large and the liver and spleen were 52 cm and 26 cm respectively. By February 1928, the swelling of the knee was tremendous with profuse discharge from several sinuses. The liver was 104 cm and the spleen 5 cm. The abdomen was very prominent with marked dilatation of the superficial abdominal veins. The urine boiled solid with albumin, the Congo Red test was positive. At this time liver therapy in doses of 4 to 8 gm three times daily was instituted.

Although the temperature was elevated and the sinuses continued to discharge up to August 1930, the child's condition showed very early striking improvement. After six months of therapy the liver was 55 cm and the spleen 28 cm, and after 2½ years (February 1930) the liver and spleen were no longer palpable. However, the Congo Red test on July 1930 still showed complete withdrawal of the dye. At the time of discharge from Neponsit Beach Hospital (August 6, 1930), to another institution, all clinical signs of amyloidosis were absent. Up to the present, six and one half years after discharge from the hospital and nine years after the institution of liver therapy, there have been no recurrences of any symptoms or signs referable to amyloid disease. Liver therapy was discontinued upon his discharge from the hospital in 1930.

Case 3 E A, male white child admitted to Neponsit Beach Hospital for Children on October 6, 1925, at the age of four years. About eight months prior to admission a diagnosis of tuberculous infection of the lumbar vertebrae was made. Fusion of the involved vertebrae by bone graft was performed at another institution. Shortly thereafter suppuration appeared in the region of the left flank and near the left anterior superior spine. The former was incised, drained and the wound sewed up. The incision soon again discharged spontaneously and continued to drain. At this stage the child was transferred to Neponsit Beach Hospital for Children.

On admission the child was in fair condition and presented a sinus in the left iliac region which discharged moderately. The condition remained unchanged until 14 months later when elevation of temperature set in associated with swelling in the right gluteal region just behind the greater trochanter of the femur. An abscess which formed was opened and drained. After discharging for a short time, it finally healed. This was followed by the formation of another abscess on the posterior surface of the right thigh, which was incised and drained.

From this point on, the temperature continued to be elevated at varying levels and the discharge from the several sinuses persisted. The child's condition became worse. Loss of weight, pallor and progressive enlargement of the abdomen, liver and spleen became apparent about two years after admission to Neponsit Beach Hospital. On August 9, 1929, when the liver was 128 cm and the spleen 6 cm, liver therapy was instituted. At first there was no definite improvement in his general appearance and condition. Within six months the liver was 9 cm and the spleen 3.5 cm. At nine months the liver edge was at 7.7 cm and the splenic margin at 2.8 cm. However, he took the liver therapy very poorly because of its unpleasant taste and

soon began to take it very irregularly, often refusing it for periods of two months. Nausea and vomiting were the chief symptoms accounting for his inability to tolerate the medication. Shortly before death which occurred on January 14, 1931, pre-uremic symptoms set in. He lapsed into a stuporous state, displaying occasional twitchings and minor convulsive seizures.

Case 4 R. H., male colored child, about seven years of age, entered Neponset Beach Hospital for Children on July 8, 1927, with Pott's disease of approximately one year's duration. Upon admission he presented an extensive kyphosis involving the fourth dorsal to the second lumbar vertebrae with a discharging sinus in the right groin at the inner side of the anterior superior spine. In addition he had chronic pan-uveitis of the right eye showing corneal and iritic opacity. There was amaurosis of the right eye. The chest was barrel shaped. The abdomen was prominent and the liver and spleen were each about 13 cm.

The child had an active tuberculous infection which varied in its severity from mild to moderate. The temperature ranged between 100 and 101° F. with occasional bouts of temperature from 102° to 103° F. The sinus in the right groin continued to drain moderately. The abdomen became progressively larger, displaying increasing dilatation of the superficial veins and enlargement of the liver and spleen. He had recurring attacks of epistaxis, edema, ascites and acquired frequent respiratory infections. By November 1929, his condition was markedly worse. The liver was down to the crest of the ilium and the spleen was 5 cm. Liver therapy was instituted but it apparently did not alter the downward course of the child. He died June 20, 1930. The entire duration of his illness, from the first symptoms of the primary disease, was about four years.

Case 5 M. N., male white child, eight years of age, was admitted to Neponset Beach Hospital on July 9, 1926. About 3½ years before, following a fall, his knee was injured and became swollen and red, but there was no complaint of pain in the hip at that time. This condition subsided and disappeared. About five months prior to admission, the boy experienced pain in the right hip with other attendant symptoms of joint involvement. At the time of entrance into the hospital, there was a large abscess on the outer side of the right thigh in the upper third. This was incised and drained, and the wound was closed. Shortly thereafter progressively increasing discharge from the wound was observed. From this time on, elevation of temperature, profuse discharge from several sinuses, anorexia, loss of weight and increasing pallor were constant symptoms. By September 1927 it was evident that the child had amyloidosis. On February 29, 1928, the liver was 8 cm. and the spleen 5.5 cm. On the latter date, liver therapy in doses of 4 gm. three times daily was given, the dose later being increased to 8 gm. thrice daily. On August 2, 1928, the bone infection was still active, but there was evident improvement in his general appearance and color. He gained in weight (11 lbs.). No ascites was observed. His liver and spleen were 4 cm. and 1.5 cm. respectively. Roentgenograms of his extremities, however, still showed progressive destruction of the head of the femur and adjacent portion of the neck and considerable involvement of the acetabulum and ilium. On May 20, 1929, his condition was satisfactory but there was still moderate discharge from numerous sinuses. Both the liver and the spleen were no longer palpable.

He continued to improve although fever and discharge from the sinuses persisted. On May 2, 1930 erysipelas set in. The course was stormy and the infection of the hip became aggravated. By January 1931, the liver was again 5 cm. and the spleen 3 cm. Within three months under continued liver therapy the liver and spleen again receded to 3.8 and 1.2 cm. However, a recrudescence of his primary disease set in and the amyloidosis advanced. In September 1931, the liver was 7.7 cm. and the spleen 5.2 cm. Shortly after this period, the parents insisted on taking him home. He was discharged against medical advice on September 28, 1931. At home he re-

cerved no liver therapy and his condition became progressively worse. He died about eight months after leaving the hospital.

Case 6 S B, male white child, 7½ years of age, admitted to Neponsit Beach Hospital for Children on May 14, 1926. About nine months prior to admission he developed a staphylococcal infection of his hand which was operated upon. Shortly thereafter he complained of pain in the right hip. He was operated upon and the hip region drained, at another institution where he resided for five months.

On admission he presented an active infection of his right hip with several discharging sinuses. This together with moderate elevation of temperature continued and by May 1928, he presented definite signs of amyloidosis. Roentgen-ray showed extensive destruction of hip joint, acetabulum, pubic bone and, in fact, almost the entire right ilium. There was marked rarefaction of the head, neck, trochanter and shaft of the femur. In February 1930, there set in an infection of the left shoulder and shortly thereafter suppuration and sinus formation ensued.

The child's condition became progressively worse. The temperature ranged between 101° and 103°, the infections in the right hip and left shoulder continued to be active and to present discharging sinuses. By July 1930, the amyloidosis was moderately advanced. The liver was 8 cm, the spleen 3.5 cm. At this time, liver therapy was instituted. Within six months there was evident improvement in his physical condition. Although the infection was still actively present in his bone, the temperature continuing to be moderately elevated and the sinuses persisting, the liver was reduced to 4.5 cm and the spleen to 2 cm. Fourteen months of liver treatment (July 1930 to September 1931) resulted in complete disappearance of both organs below their respective costal margins. However, the temperature still fluctuated between 99° and 101° F and there was still slight discharge from all sinuses. Roentgen-ray still showed activity of the tuberculous process in the bones but revealed some improvement in the appearance of several of the bones, particularly the ilium.

Liver therapy was continued and by April 27, 1932, the temperature was normal, the sinuses were healed and the bone lesions were inactive. However, the child continued to show a marked albuminuria with numerous leukocytes and many erythrocytes for several years. Complete urological examination failed to show any evidence of infection, or any other involvement of the urinary tract. The child was last seen in December 1936 when it was observed that his general physical condition was excellent, his bone condition had remained apparently healed but his urine still showed moderate albuminuria with many leukocytes and few erythrocytes. The liver and spleen could not be felt, there were no signs or symptoms to suggest amyloid disease.

Case 7 E L, male, colored child, 4½ years of age, admitted to Neponsit Beach Hospital on October 19, 1928. About two years before, following an injury, tuberculous osteomyelitis of the lower left femur and upper left tibia set in. He was at another institution during this time. On admission he displayed eight moderately discharging sinuses about the left knee joint. The latter was markedly swollen presenting a typical fusiform appearance. The abdomen was prominent with dilated superficial veins, liver was 9 cm and spleen 4.5 cm.

The temperature was elevated, rising at times to 104° F and the sinuses continued to discharge freely. By February 1929, the child's condition was very poor. He was markedly emaciated and presented marked pallor of the mucous membranes of lips, conjunctivae and finger nails. The liver was 11.5 cm and the spleen 6 cm. His abdomen was distended with fluid. At this time, liver therapy was started in doses of 4 to 8 gm three times daily. With treatment the child showed initially a very significant improvement with reduction in the size of the abdomen, liver and spleen and the disappearance of ascites. On February 7, 1930, one year after therapy had been begun, the abdomen was slightly prominent with no dilatation of the superficial abdominal veins. The liver was 2 cm, the spleen barely palpable. However,

temperature and discharge from all sinuses still continued. Roentgen-ray showed continuing activity, revealing moderate destruction of the outer condyle of the femur, and upper end of the tibia, involving the epiphyseal line and the diaphysis of the femur. One and one-half years later, the temperature became normal and there were only three discharging sinuses, the liver was just palpable. Roentgen-ray showed considerable destruction of the lower end of the femur and the epiphysis on the outer half, and moderate destruction of the epiphysis of the tibia. The patella was indistinct and irregular in outline. Two years later (February 1930), the liver and spleen were no longer palpable and all sinuses except one had healed. There now occurred a steady and definite diminution in the amount of thickening and swelling about the knee. Three and one half years after therapy had been instituted, the roentgenograms began to show healing in the knee joint. The child continued to improve and by August 13, 1934, 5½ years after the onset of the disease, and 4½ years after institution of liver therapy, the last sinus closed and remained healed.

Case 8 M M, female, white child, 8½ years of age, was admitted to the Neponsit Beach Hospital on August 14, 1929 with the history that about one year before, she struck her left thigh against an iron bar. This was followed a few days later by elevation of temperature and severe pain in the left hip. She was admitted to another institution where she was operated upon for osteomyelitis of the left femur. For about a month after the operation, the child's condition seemed to improve. At the end of this period elevation of temperature and pain in the right upper thigh recurred. A plaster spica was applied, but suppuration and spontaneous discharge from the involved area occurred shortly thereafter. Blood cultures taken with significant pyrexia always showed abundant colonies of *Staphylococcus albus*.

The child was admitted to Neponsit Beach Hospital in very poor condition. She was thin and pale. In the region of the great trochanter on the left side, there were two discharging sinuses, and three sinuses were present near the trochanter on the anterior surface of the right thigh. During her residence in the hospital, the child displayed a relapsing course. At irregular periods, a new focus of infection arose, or a previous one became active. On each occasion, fever of varying degree, pallor, loss of weight, prostration, anorexia, etc. were manifested. The infection either subsided spontaneously in the course of time or progressed to local suppuration. Blood cultures taken on several of these occurrences were positive for *Staphylococcus albus*. Several blood transfusions were administered.

With repetitions of the active infections the child became progressively worse. By May 1930, definite amyloidosis may be said to have set in. By January 1931, the child was markedly pale and emaciated with abdominal enlargement and dilated superficial abdominal veins. The spleen and liver were enlarged to 5.5 cm. and 8 cm. respectively. On January 14, 1931, liver therapy was instituted.

Although the child's infection continued to be of a relapsing nature, with liver treatment the child showed definite improvement of her amyloidosis. After one year of therapy, she had gained seven and one-half pounds and the spleen was 20 cm., the liver 3.8 cm. No ascites was present. Two years of therapy resulted in decrease of the size of the liver to 1.5 cm. and of the spleen to the point where it was barely palpable. Within three years, there was no objective evidence of amyloidosis except for such symptoms as pallor and albuminuria. The chronic osteomyelitis, however, continued to be active and the child was transferred to another institution on December 3, 1934 in order to obtain surgical treatment. At the latter institution an extensive operation was performed. After an irregular course the bone infection subsided and has remained inactive to date.

Case 9 F S, female white child, aged 5 years, admitted to Neponsit Beach Hospital on September 11, 1929 because of tuberculosis of the left hip, the onset of which had occurred on November 14, 1927. She was treated by immobilization in a cast. About one month prior to admission gross suppuration set in. This was in-

cised and drained. On admission the child was thin, pale, and displayed a very active destructive tuberculous infection of the left hip with several discharging sinuses.

Since her admission, the temperature had constantly been elevated, ranging usually between 101 and 102°, but often rising to heights of 103 to 104° F, the sinuses continued to discharge freely and two new areas of suppuration developed. Roentgen-ray on January 8, 1931 showed considerable destruction of the acetabulum and head and adjacent portion of the neck of the left femur. The first evidence of amyloidosis was noted by May 1930. On January 20, 1931 when liver therapy was instituted the abdomen was very prominent. The liver and spleen were both 3 cm. Within 1½ years there occurred such complete recession of the liver and spleen that each organ was no longer palpable.

The child's infection, however, continued to run an active course with persistence of discharging sinuses, fever and symptoms in the left hip joint. Anorexia, loss of weight, weakness and pallor continued. On June 1, 1934 the liver and spleen again began to enlarge. The liver was 1.5 cm, the spleen barely palpable. On October 22, 1935, the liver was 5.5 cm, the spleen 4 cm. Persistence in administering liver therapy led eventually to recovery so that, in spite of the continuing active infection, by July 10, 1936, the liver had receded to 2.5 cm, and the spleen to 1.5 cm. On October 15, 1936, the liver was 2 cm and the spleen was just palpable. Liver therapy was discontinued for two months (October 15 to December 11, 1936) and it was observed that her liver increased to 7 cm and the spleen to 2 cm. The liver product was therefore resumed again resulting in striking reduction in the size of both organs to 2.5 cm and 1.5 cm respectively. The status of the tuberculous infection had not varied in its severity during these latter periods.

Case 10 T. F., male, white child, 8 years of age, admitted to Neponsit Beach Hospital on June 3, 1932, with the diagnosis of tuberculosis of the left hip of about four years' duration. On January 25, 1932, an extra-articular fusion of the left hip was performed at another institution. On April 26, 1932 the temperature rose to 104° F, the wound began to discharge.

On admission the child appeared pale and was poorly nourished and developed. He presented a large granulating T-shaped wound over the left hip and ilium. It was noted that the abdomen was distended but the liver and spleen were not palpable.

Temperature continued to run as high as 102° F nearly every afternoon. On October 24, 1932, the roentgen-ray showed extensive destruction about the head of the left femur and acetabulum. The liver and spleen were now both palpable. With continuance of the moderate pyrexia and active infection about the left hip, including profuse discharge from the sinuses, the abdomen, liver and spleen increased progressively in size. On March 3, 1933, he was markedly emaciated and pale, the liver and spleen were each 5 cm. Liver therapy was then instituted.

The tuberculous infection continued to be very active. Six months after liver treatment (September 15, 1933) had been started, the liver had increased to 7.5 cm although the spleen remained at 5 cm. Roentgen-ray showed a more extensive involvement and destruction of the left acetabulum, femur and ilium. One year of therapy resulted in a definite improvement in the amyloidosis in spite of the active hip infection. The liver and spleen were each 2.5 cm. The temperature continued to be elevated and the sinuses to drain profusely. By August 1934 or about 1½ years later, the liver had enlarged to 5 cm and abdominal ascites was present. Persistence of liver therapy led to slow but steady improvement. In spite of the relapsing nature of his primary infection, two years later on March 5, 1935, the waxy pallor, enlargement of the abdomen, prominence of the superficial abdominal veins, etc. were absent. The liver, however, was 4 cm and the spleen 1.5 cm. There was no ascites. One year later, in March 1936, the liver was 2.5 cm, the spleen 1 cm. Temperature now ranged between 100° and 101° F and discharge from the sinuses was less. Liver therapy was discontinued in July 1936 when both

organs were just palpable. On October 15, 1936, there was slight discharge from the sinuses about the left hip. The liver and spleen were no longer palpable. Examination on February 11, 1937 revealed no objective evidence of amyloidosis.

Case 11 E Z, male white child, aged 10 years, admitted to Neponsit Beach Hospital for Children on July 15, 1930. Three years before the child had injured his right lower extremity. A nurse noticed the child limping on the street and induced the mother to bring the child to a hospital for treatment. On May 31, 1930, the child was examined at a hospital where extensive destructive disease of the right hip was noted. Stretching was done preliminary to an extra-articular fusion. The latter was performed on June 30, 1930.

Child was admitted in very poor condition, thin and looking pale. The abdomen was not prominent, the liver and spleen not palpable. Urine examination was negative. In the hospital the temperature was moderately elevated, and there was considerable discharge from two sinuses. On January 9, 1931, definite signs of amyloidosis were observed. The liver and spleen were each 1 cm. Roentgen-ray showed marked destruction of the femoral head and acetabulum. The condition became progressively worse so that by September 11, 1931, the signs of amyloidosis were advanced. The child presented a striking waxy pallor and was very emaciated. The abdomen was markedly distended with fluid, both legs and feet were edematous. The liver was 5.3 cm, the spleen 3 cm. Roentgen-ray showed increased destruction in the region of the acetabulum. Liver therapy was instituted. The amyloid condition continued unchanged except for the disappearance of the edema of the lower extremities and a significant decrease in the ascites. On January 19, 1932, there was marked thickening and enlargement of the right hip with a reddened area and slight fluctuation over the right ilium. The size of the liver and the spleen had diminished to 4 cm. The incitant tuberculosis continued very active.

With slight fluctuations in the course, the status of the amyloidosis remained unchanged until July 1934 or about three years after the institution of treatment. Although the temperature was still elevated, the sinuses continued to discharge profusely, and roentgenograms showed increasing involvement of the right ilium and moderate involvement of the head and neck of the femur, the enlargement of the abdomen was now only moderate and the liver and spleen were 5 cm and 1.5 cm respectively. For the next year and one half (or until January 1936) the child's symptoms and roentgenologic findings remained unchanged. On the latter date, the liver was 4 cm, the spleen 1.3 cm. Roentgen-ray showed now marked destruction of part of the right ilium, upper end of the femur, pubis and ischium with considerable distortion of the pelvis. What remained of the neck of the femur was still in the acetabulum, marked adduction and flexion were present. The active symptoms of the primary infection continued unabated. The condition of the amyloidosis, particularly in the liver and spleen, varied. In July 1936, after five years of treatment, the liver was 3 cm, the spleen 1.3 cm. Liver therapy was discontinued on the latter date to note the effect of such a procedure. On October 10, 1936 the liver and spleen were 6 cm and 1.5 cm respectively. Liver treatment was resumed and on January 26, 1937 the patient's liver was 4 cm, his spleen 1.5 cm. Moderate discharge from the sinuses and temperature elevation were still present. On May 21, 1937, both the liver and spleen were just palpable. All other signs of amyloidosis were absent.

Case 12 V C, male colored child, 10 years of age, admitted to Neponsit Beach Hospital on May 12, 1934. Following an injury in March 1933, the child experienced pain in the right sacroiliac joint. About one month later, a soft fluctuant mass developed and was aspirated. A plaster spica was applied giving the patient comfort for a time. Soon, however, the abscess again broke down, roentgenograms and guinea pig tests at this time were positive for tuberculosis. The child continued to run a spiking temperature. The plaster was changed at intervals of 8 to 10 weeks.

On admission the child appeared emaciated, pale, with a prominent abdomen and a liver and spleen that were just palpable. There was a huge granulating area over the right great trochanter four inches square, bathed in pus. There was also one of similar size near the crest of the right ilium and in the right groin there was a profusely draining sinus.

The temperature was irregular and remittent. The patient's condition became rapidly worse. Roentgenograms showed marked rarefaction of all the bones of the right femur and ilium. On November 30, 1934 the liver was 3 cm, the spleen 1.5 cm. Liver therapy was instituted at this juncture. During the first three months of treatment there was slight improvement in his physical appearance. With the continuance of the severity of his primary condition and his inability regularly to take the liver preparation without vomiting, his condition became worse. On November 1935, the liver and spleen were 8 cm and 5 cm respectively. However, he showed irregular periods of improvement in the amyloid condition, each lasting one to three months. His tuberculous infection continued unabated. In May 1936 after about 1½ years of inconstant liver treatment, the abdomen became very prominent and marked ascites set in. In addition the liver and spleen had increased to 9 cm and 6.5 cm respectively. Roentgen-ray showed a considerable area of disease involving the right ilium, ischium and femur down to the middle third of the shaft. He died on February 14, 1937.

Case 13 C. C., female white child aged 11 years, was admitted to Neponset Beach Hospital on May 9, 1935. About six years before, child had had Pott's disease and had been placed on a Bradford frame for six months and then in a cast for over a year. At the end of this time the tuberculous disease of the spine was apparently quiescent and had continued inactive to the date of admission. Three years before she experienced pain in the left hip. She was immobilized in a plaster spica cast until the fall of 1934 when it was removed and she was allowed to be up and about. Several months later the activity in the left hip recurred. Suppuration and discharging sinuses developed.

On admission the child was very pale and thin, weighing 53 pounds. She showed classical signs of amyloidosis. The liver and spleen were 1 cm. The left thigh was in flexion and adduction and presented about it numerous discharging sinuses. Shortly after admission the child's condition became progressively worse. On September 19, 1935, the liver was 8 cm, the spleen 5 cm. Roentgen-ray showed marked adduction and vacuolization in the shaft, neck, head and great trochanter of the left femur. There was apparently no pelvic wall left to the hip joint. Liver therapy was then instituted. Her amyloid condition improved slowly with short periods of remission. On March 13, 1936 the general condition was fair. The liver and spleen were 5 cm and 2 cm respectively. Roentgen-ray showed greater destruction of the acetabulum, head, neck and great trochanter of the left femur than was present in the previous plates. A rather large vacuole was present at the junction of the great trochanter and the shaft. The temperature continued to be moderately elevated and her sinuses discharged profusely. She soon began to object to the liver therapy and vomited frequently. As a result she took very little liver. By October 15, 1936, it was noted that the liver was 6 cm and the spleen 4.5 cm. She left the hospital against advice shortly thereafter (November 8, 1936).

COMMENT

Thirteen children with moderately advanced to advanced amyloidosis have been treated with a desiccated powdered whole liver product administered in a suitable vehicle in doses of 4 to 8 grams, three times a day. The children as a rule tolerated the liver preparation fairly well. There

TABLE I
Summary of Results with Liver Therapy in Secondary Amyloidosis

Case	Age at Onset of Primary Disease (Years)	Nature of Primary Disease	Duration of 1° Disease to Time of Appearance of Amyloidosis (Years)	Duration of 1° Disease After Onset of Amyloidosis (Years)	Age at Onset of Amyloidosis (Years)	Duration of Amyloidosis Before Treatment (Years)	Duration of Amyloidosis During Treatment (Years)	Results of Liver Therapy in Individual Cases	Remarks
1	7	Tbc spine	4	5	11	3	2	Cured	Subsidence of amyloid slow improvement in 1° disease
2	7½	Tbc knee	2	4	9	1½	2½	Cured	Ditto
3	3½	Tbc spine	2½	3½	6	1½	1½	Died	Liver therapy taken irregularly and poorly
4	6(?)	Tbc spine	1(?)	3	7	2½	3½	Died	
5	7½	Tbc hip	1½	4½	9	1½	3½	Died	Left hospital and received no therapy for 8 months
6	7	Tbc hip	2½	4	9½	2	1½	Cured	1° infection active for nine months after cure of amyloidosis
7	2½	Tbc knee	1	6½	3½	1½	2	Cured	1° infection was present for 3 years after cure of amyloidosis
8	7½	Multiple chronic osteomyelitis	2½	5½	10	¾	3	Cured	1° infection was present for one year after cure of amyloidosis
9	3	Tbc hip	2½	7*	5½	¾	6½*	Much improved	1° infection still present and active
10	4	Tbc hip	4½	4½*	8½	1½	3½-4	Cured	1° disease still present and active
11	7	Tbc hip	3½	6½*	10½	1½	5½*	Much improved	1° infection still active, liver and spleen just palpable
12	9	Tbc hip	1	2½	10	1	2½	Died	Took liver therapy poorly and irregularly
13	8	Tbc hip	3	2*	11	1½	1½	Condition unchanged	Discharged against advice

* Disease still present Duration specified is that up to May 1937

were a few, however, who were unable to take this medicament continuously. Frequently nausea and vomiting set in and forced the discontinuance of its use for periods varying between 14 days to two or three months. It was these children, too, who did not show the striking benefits that were evident in the others. A summary of the results is recorded in table 1.

Complete recovery from generalized secondary amyloidosis was obtained in six of the juvenile patients. With the exception of two phenomena, i.e. albuminuria and the Congo Red test, all other signs and symptoms indicative of the existence of amyloidosis disappeared completely within an average period of two to three years after institution of liver therapy. These children are today alive and well with no recurrence of symptoms after a lapse of two to five years or more. In two other children there has occurred to date significant clinical improvement and all indications point to complete recovery in the near future.

In one subject who received the liver therapy for only 13 months, the lardaceous condition has remained essentially unchanged. The situation was somewhat complicated by the fact that she was taking the preparation very irregularly due to its unpleasant taste and the development of nausea and vomiting.

The remaining four children died. Two of them (cases 3 and 4) were in a very advanced state of amyloidosis and received the product irregularly only over a period of 16 and 7 months respectively. Even in these cases there was improvement in the amyloid state as evidenced by the disappearance of edema and ascites and by the diminution in the size of the liver and spleen. However, the severity of the primary condition was responsible for the fatal termination. In the third child (case 5) there occurred significant improvement. After 15 months of liver therapy, the liver and spleen were no longer palpable. With the advent of erysipelas, the tuberculous infection and the amyloidosis were both aggravated. The severity of the primary disease retarded the amelioration of the amyloidosis by liver therapy. The child's condition was unimproved at the time of his discharge from Neponsit Beach Hospital. His parents insisted upon taking him home. He died within eight months after his return home. No liver therapy was given during his stay at home.

The fourth child (case 12) had a malignant tuberculous infection. This, coupled with his inability to take the liver therapy, was probably responsible for our failure. The unavailability of a potent liver extract for parenteral administration was the reason for not using such a preparation in the cases that objected to taking the medicament orally.

The primary disease in all these children was very severe. Symptoms indicating activity of the infection, e.g. fever, continued increasing destruction of bone, discharging sinuses, local pain, tenderness, limitation of motion and pain upon movement, were present during the period of treatment and continued for a considerable time even after striking recession of the symptoms of amyloidosis. In four patients who recovered from their amy-

loidosis, elevation of temperature, considerable discharge from sinuses and local signs of active infection persisted for periods of from eight months to three years after clinical cure of the amyloid state was obtained. In the other children, definite retrogression of the amyloid symptoms occurred even during the height of the initial infection. These observations speak against the suggestion that improvement of the amyloid state is attributable to improvement of the concurrent tuberculous condition. The improvement of the amyloidosis and the evidences of its apparent resorption preceded by months or even years the improvement in the primary infection, although the latter did, in time, occur. Such improvement of the primary infection is to be expected in view of the fact that the existence of amyloidosis aggravates the initial disease and that the degree of severity of the latter would decrease with melioration and removal of the lardaceous material. To disregard these clinical manifestations and to attribute the favorable clinical course of the treated amyloidotic children to the subsidence of the primary disease and not to the liver therapy we therefore believe is unwarranted. Rosenblatt¹³ citing a case of recovery, which was treated with a liver product and in which the primary disease showed almost simultaneous improvement, ascribes the results solely to the subsidence of the underlying condition. This interpretation is based on his conception that amyloidosis simply reflects a very advanced state of the initial disease, but that the lardaceous condition per se does not exercise to a significant degree any serious effect upon the organism. This stand is untenable in view of the marked renal, gastrointestinal, hepatic, hematological and chemical functional disorders and the organic changes which are present in generalized primary and secondary amyloidosis. Further, in our series of 68 cases of amyloidosis, receiving no liver medicament, all died within two to three years.¹⁴ Autopsy in most instances of this group indicated that the amyloidosis rather than the underlying tuberculous infection was directly responsible for the fatal outcome. In fact, the tuberculous process in such patients was distinctly less extensive and severe than it was in a comparable series of non-amyloidotic subjects in whom death was the direct result of the acid-fast infection. Similar observations, that the degree of amyloidosis and its fatal effects are not dependent on the extent or severity of the incitant tuberculosis, have recently been made independently by Lipstein and Auerbach.¹⁷

In the treated group, in addition to the six cases of recovery after the onset of the amyloid condition, the rest showed considerable prolongation of their survival period. This in itself indicates a marked retarding effect of the liver preparation upon the lardaceous process and is in harmony with the observation that white mice show definite retardation and resorption of the amyloid with the use of the liver product.^{15, 16}

Very soon after the institution of the liver therapy, striking improvement of the amyloidosis was observed in all cases. At the beginning of the therapy, for short periods varying from three to six months, the im-

provement was more marked. It then continued at a much slower rate either with steady progress or with periods of remission. In some instances, the relapses were of the same magnitude as the illnesses preceding treatment. Persistence of the liver medicament, however, led to amelioration or recovery from amyloidosis in most instances. This point is worth stressing. One should not be discouraged at failure to obtain uninterrupted improvement. One should not suspend treatment when one encounters severe recrudescence of amyloidosis even though it may be of long duration. Persistence in therapy over a period of several years may eventually result in recovery. When one realizes the vagaries of the primary disease constantly operating to effect amyloid formation, one cannot always expect uninterrupted improvement.

The first evidences of improvement of the amyloidosis are a reduction in the size of the abdomen and of the liver and spleen, and the diminution of the dilatation and tortuosity of the superficial epigastric veins. Subsequently there occurs improvement in the general condition and appearance of the patient including the color of the skin and mucous membranes. After the initial subsidence of the various manifestations of amyloidosis, there will be a relatively longer period of one or more years when the signs may remain practically unchanged or may recede very slowly. In the event of a severe and prolonged relapse of the primary disease, many of the symptoms may return and even become aggravated. With continuance of liver therapy, total recession will probably take place.

A possible explanation for the early more rapid retrogression of the lardaceous condition may be that the more recently formed amyloid is less stable and resistant to physico-chemical influences and is more rapidly resorbed. It is possible that it is this relatively newly deposited substance which is at first removed. On the other hand the longer the amyloid resides in the tissue, the more stable does it become^{16, 18}, and the more difficult does it become to disintegrate and eliminate this material. This may account for the apparent retardation during the second stage in the resorption of amyloid.

The marked albuminuria which has been present in all the treated children persisted in most cases long after the complete disappearance of the other signs and symptoms of amyloidosis. Usually not until two to five years had elapsed after apparently complete clinical recovery, did the urine become free from albumin. The quantitative decrease proceeded at a very slow rate. The persistence of the albuminuria after clinical recovery from amyloidosis, is, in most instances, probably due to the continuance of the primary disease. One of our children (case 6) still has marked albuminuria with numerous leukocytes and an occasional erythrocyte in his urine four years after the total disappearance of all other signs of amyloidosis. He is apparently in good health and complete examination including an extensive genito-urinary investigation fails to reveal any other

condition to account for this phenomenon except possibly structurally altered kidneys, the after effects of renal amyloidosis

The Congo Red test was positive (100 per cent withdrawal) in all the treated children before institution of liver therapy and in recovered cases, even at the time when there were none of the other symptoms or signs of amyloidosis. In two subjects in whom repeated Congo Red tests were performed, there was a gradual decrease in the percentage withdrawal of the dye from the blood stream. In both patients the sharp reduction in the dye absorption occurred only after the disappearance of the primary disease. However, within 16 months after the latter phenomenon, the test was completely negative (i.e. 100 per cent retention of Congo Red in the blood stream). In passing, it may here be said that the presence of Congo Red absorption of even 70 per cent of the injected dye has been reported in cases without amyloidosis as proved by detailed autopsy examination¹⁷. Three such cases showed 90 to 100 per cent withdrawal of the dye. The Congo Red test must therefore be considered of less significance in the diagnosis of amyloidosis, in the absence of signs and symptoms of the disease, than is generally accepted.

The very marked anemia which usually is present in these children became less severe but never quite disappeared until recovery was complete. The blood-chemical findings of decreased total serum protein and inversion of the albumin-globulin ratio, obtained in all cases of amyloidosis, returned to normal values very slowly after other clinical symptoms had disappeared. In one case (case 7) a return to normal was observed only four years after clinical cure. The primary infection is in the main responsible for the persistence of the anemia and the serum protein changes.¹⁹

DISCUSSION

The earliest stages of amyloidosis cannot be determined clinically with certainty. It is often a matter of guesswork. It is probable that the initial changes are those which are common to all infections and that gradually with continuance of the underlying cause, changes develop further until they reach the transformation which is known pathologically as amyloid. Even at this point the process does not stop. This process, except possibly in the very advanced stages, may be reversible. With the disappearance of the causal factor and provided no permanent secondary changes have occurred, amyloid may be resorbed and complete recovery may follow. This is substantiated by animal experimentation¹⁰ and by clinical reports of cures¹⁻¹³. There has been one drawback to the above concept. Once unquestioned advanced amyloidosis had set in, the condition invariably seemed to progress to a fatal termination. This is indicated by the very few reported cases of recovery in the literature. This outcome is the result of two reciprocally acting factors. Amyloidosis occurs in severe and prolonged infections which run an unabated course and in themselves cause death, and secondly

the occurrence of the lardaceous condition not only aggravates the primary disease but causes great functional disturbances in the individual, reducing his vitality and general resistance. It is for these reasons that a steady unfavorable march of events is noted in almost all cases of amyloidosis.

In order to prevent any possible criticism of our results with the 13 treated children, only those subjects were selected who had pronounced symptoms of amyloidosis, which definitely progressed during the control period of six or more months, and whose primary disease was active and was not responding to any of the other measures. It was with the intention of making certain that no other factor, except the liver therapy, could possibly be considered as instrumental in influencing the course of the disease. Previously all our cases of amyloidosis although under identical management except for the liver administration, died. The six cases of complete cure, and the two children with substantial improvement, indicate definite benefit that is to be derived from liver medicament. Furthermore, definite prolongation of survival period in those others who died with some amelioration of their amyloid condition, indicated a favorable influence of the remedy. That resorption of amyloid occurs even during the active phase of the primary disease as indicated by elevation of temperature, discharging sinuses, local symptoms and roentgen-ray findings of progressive destruction, must lead one to attribute a beneficial effect of liver therapy upon generalized secondary amyloidosis.

Parenthetically it may be added that more cases of recovery with more rapid resorption of amyloid would probably have occurred if the subjects chosen for treatment had not been so severely affected or had not been allowed to progress untreated for so long a period. Furthermore, although such studies are difficult to evaluate, prevention of amyloid formation may be possible by administering liver therapy to patients with severe suppurative primary infection. The results in three such selected children tended to indicate such an effect. All these probabilities are indicated both by the results obtained in this study and by previous animal experiments with early amyloid.¹⁶

Organotherapy consisting chiefly of liver, spleen or bone-marrow feeding has been used by many workers in the treatment of tuberculosis and other chronic infections. Ruttgeis and Kamsler,²⁰ Loeffler,²¹ Ropschitz,²² Kuss,²³ Fliegel,²⁴ Armand-Delhile²⁵ fed raw spleen and obtained good results in the treatment of children with extensive tuberculosis of the bones and joints. Similar beneficial effects and rapid improvement with the use of splenic extracts were noted by Bayle²⁶ and Dunham.²⁷ Dejust-Defives²⁸ found that the administration of combined extracts of liver, spleen and kidneys to tuberculous patients resulted in remarkable improvement of the blood and the general condition. Experimental confirmation of the usefulness of splenic extract in guinea pigs infected with tubercle bacilli was obtained by Bayle²⁶ and Watson.²⁹ Newton³⁰ observed favorable influence

upon the general condition, appetite and blood of tuberculous patients receiving liver extract. Faust and his co-workers³¹ have shown that feeding of raw liver or a powdered liver extract to dogs infected with *Endameba histolytica* exercised a decidedly ameliorative effect. Becker and Morehouse³² by administering dried powdered liver retarded the development of coccidian infections in rats and chickens fed with oocysts.

Many workers have stressed the rôle of the reticulo-endothelial system in infections. The condition of this important specialized tissue which is scattered throughout the body but is predominant in such organs as the liver and spleen, is a very important determining factor in the treatment of infectious disease, particularly of tuberculosis. Any measure that would increase its functional action or supplement it qualitatively should enhance the organism's ability to cope with the infection. With this view in mind Wedekind³³ advocated the intravenous administration of a suspension of fine particles of carbon in sub-toxic doses in the treatment of pulmonary tuberculosis, and Schurer-Waldheim³⁴ proposed irradiation of the spleen. Schliephake and Sincke³⁵ noted that the administration of splenic extract to rats and guinea pigs increased the storage capacity of the reticulo-endothelial system for trypan blue. These agents as well as others stimulate the reticulo-endothelial system or caused the production of hypertrophy and hyperplasia of the elements of this system, a stage morphologically which precedes the appearance of experimentally produced amyloid (so-called precursory stage).¹⁰

Amyloidosis can be produced in certain animals by the parenteral injection of a variety of substances.³⁶ These animal studies shed much light on the nature of this pathological condition. Several theories are advanced by respective workers.³⁷⁻⁴¹ Without engaging in any discussion of the relative merits of each, the authors wish to offer one that appears most plausible to them, based on the work of others as well as their own. A more detailed discussion of it appears in other publications.^{14, 16}

Amyloidosis is the result of a relatively long-continued disturbance of endogenous protein metabolism. In any condition where there occurs persistently an excessive destruction of tissue protein, such as during chronic infections or wasting diseases, amyloidosis may set in. Exogenous protein metabolism is performed by the alimentary tract and its accessory organs such as the liver, etc. The tissue cells also participate in this process. However, it is the gastrointestinal tract with its wealth of chemical substances that, in the main, disintegrates the large protein bodies into small and assimilable compounds. With few exceptions, the gastrointestinal system can adapt itself and can, relatively easily, digest indefinitely varying amounts of protein material. In the matter of endogenous protein metabolism, the human being and most animals have not such relatively unlimited powers. The metabolic products consist of different protein fractions, many of which are not of a chemical form which can be assimilated, utilized or eliminated without further bio-chemical action. While the tissue

cells do possess enzymes and other lytic agents, they are limited in this respect both qualitatively and quantitatively. However, this shortcoming is to a great extent overcome by the reticulo-endothelial system. The latter, with its wealth of specialized cells, has the capacity of taking up (phagocytizing) these non-utilizable products and altering them into chemical forms which can be metabolized by the tissue cells or of retaining these so-called foreign substances, thereby permitting their original elimination without unduly disturbing the organism. This remarkable reticulo-endothelial system can undergo hypertrophy and hyperplasia in response to such increased demands. Although its reserve power is great, this hypertrophy and hyperplasia cannot go on indefinitely. A point is eventually reached when it decompensates though this may vary greatly with the individual.

In any condition where excessive destruction of tissue protein occurs, such as in chronic tuberculosis, the organism is called upon to take care of the various kinds of split protein molecules. The reticulo-endothelial cells, playing an active rôle in this endogenous metabolic process, are at first able to dispose of these substances with relative ease. As this demand continues or increases over a very long period of time, the phagocytic cells begin to lag or are unable to take care of the material as fast as it is being formed. At this stage increasingly larger masses of the material reside in each cell until these fuse with one another forming giant cells which finally disintegrate and, together with the amyloid substance, form extra-cellular deposits. The exhaustion or the inability (decompensation) of the fixed and wandering cells of the reticulo-endothelium to cope with the demands causes further extra-cellular deposition. Hypertrophy and hyperplasia cannot continue indefinitely. Phagocytosis cannot keep pace with the continued supply of newly liberated protein. Eventually the excessive accumulation of this material interferes with the function of the organ where it resides, produces a slow but progressive atrophy, and finally a necrosis of the normal tissue with resultant somatic death.

The action of the liver substance in its favorable effect upon resorption of amyloid may be one of supplementing the important component or components which are necessary for the continuance of this reversible process, or it may stimulate further the reticulo-endothelial system, or in some other unknown manner it may affect endogenous protein metabolism. It is significant that in animal experiments liver extract produced marked reticulum cell hyperplasia.

To ascribe amyloidosis merely to a hyperproteinemia is to disregard consideration of the dynamics of its formation and to overlook the possibilities of therapy which attention to the reticulum cell changes suggested experimentally to others⁴² and to ourselves, and which the present report of the cases treated and cured by the use of the reticulum cell enhancing agents strongly confirms.

Aside from all theoretical considerations, the present study indicates that amyloidosis complicating chronic suppurative disease is, in human

beings, a clinically reversible process in all but the extremely advanced phases. True, one must stubbornly persist in using liver therapy, but with such or similar therapy, it is no longer necessary to view cases of recovery from amyloid as isolated and unusual as has been the opinion hitherto. And it is no longer necessary to regard this disease as incurably progressive. The experimental evidence previously reported and the treated cases reported here indicate that amyloid may be a curable malady.

SUMMARY

1 Thirteen cases of amyloidosis secondary to chronic suppurative disease in children were treated with oral administration of powdered whole liver extract. Of these, six cases have now been completely free of all clinical signs of amyloid for periods of from eight months to six years. Two patients have shown enormous improvement. Four children in advanced stages of amyloid and tuberculous disease when first seen have died. These four took the liver preparation very poorly and irregularly. Two of the dead subjects were in an extremely advanced state and died very shortly after the institution of therapy. One child, whose amyloidotic condition was essentially unchanged, left the institution before a sufficient period of therapy had elapsed.

2 The clinical improvement of the amyloid state occurred during the presence of the active suppurative infection, and the clinical cure preceded, by a very substantial interval as a rule, the subsidence and disappearance of the primary disease.

3 Emphasis is laid upon the fact that liver therapy must be persistently employed, despite absence of clinical improvement, for periods of three or more years before failure is admitted. It is pointed out that clinical amelioration of the amyloidosis is not regularly progressive and it is suggested that this may be a function of the variable chemical composition of amyloid of different ages, as well as of the relapsing nature and severity of the primary incitant infection.

4 Diminution in the size of the liver and spleen are usually the first signs of improvement under therapy. The other symptoms recede slowly.

5 The rôle of the reticulo-endothelial system and disturbance of endogenous protein metabolism in the formation and resorption of amyloid are discussed and a theory is advanced as to the mechanism involved. The rôle of the liver product in the resorptive process, as a factor in this mechanism, is indicated.

6 It is pointed out that amyloidosis is a reversible process. Experimental evidence and the here reported cases of recovery indicate that amyloidosis is a curable malady.

Note In the year that has elapsed since this paper was submitted for publication, cases 9 and 11 (table 1) have been completely cured of all signs of amyloid disease and are entirely symptom-free as far as this disease is concerned. The tuberculous sinuses, however, are still draining profusely, their temperature continues elevated,

and the roentgenograms show increasing bone destruction. The other living cases have remained entirely free from signs or symptoms of amyloid disease without further liver therapy except in case 10 where, because of continuing activity of considerable degree of the tuberculous process, liver therapy is still being used. To the combined figures in the columns (table 1) labelled "Duration of Amyloidosis Before Treatment" and "Duration of Amyloidosis During Treatment," i.e., length of survival after the diagnosis was established, one year should be added in the cases 1, 2, 6, 7, 8, 9, 10, and 11.

BIBLIOGRAPHY

- 1 KRETZSCHMAR, P. H., and WESTBROOK, B. F. A case of chronic empyema with extensive amyloid degeneration—recovery, *Proc Med Soc County Kings*, 1880, v, 343
- 2 OWEN, I. Recovery from advanced lardaceous disease, *Proc Med Soc London*, 1886, ix, 18
- 3 GAIRDNER, W. P. In discussion of F. Delafield's paper "On the diseases of the kidneys, popularly called Bright's disease," *Trans Assoc Am Phys*, 1891, vi, 149
- 4 HARRINGHAM, W. P. *Kidney diseases*, 1912, Oxford University Press, Oxford, page 353
- 5 NATHAN, M. Ueber die klinische Diagnose mittels Kongorotinjektionen, *Munchen med Wchnschr*, 1928, lxxv, 1883
- 6 WALDENSTROM, H. On the formation and disappearance of amyloid in man, *Acta clin Scandinav*, 1928, lxiii, 479
- 7 WALKER, G. F. A case of recovery from amyloid disease, *Lancet*, 1928, ii, 120
- 8 GRAYZEL, H. G., JACOBI, M., MASLOW, H., and WARSHALL, H. B. Experimental studies in amyloidosis, *Proc Soc Exper Biol and Med*, 1930, xxxviii, 172
- 9 WHITBECK, B. H. Liver meal in the treatment of amyloidosis in surgical tuberculosis, *Jr Bone and Joint Surg*, 1932, xiv, 85
- 10 HABEIN, H. C. Amyloidosis: report of a case in which the patient recovered, *Proc Staff Meet, Mayo Clinic*, 1934, ix, 261
- 11 REIMANN, H. A. Case of amyloidosis with recovery, *Jr Am Med Assoc*, 1935, civ, 1070
- 12 KENNEDY, W. R. Renal amyloidosis, *Canad Med Assoc Jr*, 1935, xxxiii, 385
- 13 ROSENBLATT, M. D. Recovery from generalized amyloidosis secondary to pulmonary tuberculosis—report of a case, *Arch Int Med*, 1936, lxvi, 562
- 14 GRAYZEL, H. G., and JACOBI, M. Generalized amyloidosis secondary to tuberculosis (To be published)
- 15 GRAYZEL, H. G., JACOBI, M., WARSHALL, H. B., BOGIN, M., and KRAMER, B. Clinical and experimental studies in amyloidosis, *Acta Paediat*, 1933, xxvi, 177
- 16 GRAYZEL, H. G., JACOBI, M., WARSHALL, H. B., BOGIN, M., and BOLKER, H. Amyloidosis: experimental studies, *Arch Path*, 1934, xlvii, 50
- 17 LIPSTEIN, S., and AUERBACH, O. Congo Red test, *Quart Bull Sea View Hosp*, 1937, ii, 120
- 18 WELLS, H. G. *Chemical pathology*, ed 5, 1925, W. B. Saunders Company, Philadelphia
- 19 GRAYZEL, H. G., JACOBI, M., and MILLER, P. (To be published)
- 20 RUTTIGERS, P., and KAMSLER, A. Über Milzdiät bei Tuberkulosen, *Beitr z Klin d Tuberk*, 1929, lxxii, 68
- 21 LOEFFLER, F. Milzverfütterung bei eitrigen Knochen- und Gelenkerkrankungen, *Zentralbl f Chir*, 1929, lvi, 2946
- 22 ROPSCHITZ, A. Über eine bequeme Durchführungstechnik der Rohmilztherapie bei destruktiver Gelenktuberkulose, *Med Klin*, 1930, xxvi, 166
- 23 KUSS, H. Milztherapie bei Knochen- und Gelenktuberkulose, *Med Welt*, 1929, iii, 1334
- 24 FLIEGEL, O. Calf spleen diet in treatment of suppurative tuberculosis of joints, *Jr Bone and Joint Surg*, 1930, xii, 788
- 25 ARMAND-DELLILE, P. F. Action favorable d'extraits spléniques sur certaines formes évolutives de la tuberculose pulmonaire chez l'enfant, *Rev d 1 Tuberc*, 1928, ix, 256

- 26 BAYLI, J C L'Opothérapie splénique Traitement de choix de la tuberculose, Presse Med, 1925, lxxvi, 1266
- 27 DUNHAM, R W The effect of splenic extract and bone marrow on the blood picture in pulmonary tuberculosis, Am Jr Med Sci, 1925, clxx, 394
- 28 DEJUST-DRIFVES, S Étude clinique de l'action simultané des extraits foie, rein, rate sue diverses anémies (Anémies post-hémorragiques Anémies de la tuberculose), Progres Med, 1930, lvi, 189
- 29 WATSON, G F Raw spleen extract in tuberculosis, Am Rev Tuberc, 1935, xxxii, 312
- 30 NEWTON, H F Über die Beeinflussung sekundärer Anämien bei Tuberkulosen durch Leberextrakte, Klin Wchnschr, 1928, vii, 1062
- 31 FAUST, E C, and SWARTZWELDER, J C Use of liver extract intramuscularly in the course of acute amebiasis in dogs, Proc Soc Exper Biol and Med, 1936, xxxviii, 514
- 32 BECKER, E R, and MOREHOUSE, N F Liver as a source of vitamin G, Science, 1936, lxxxiii, 530
- 33 WEDEKIND, T Die Bedeutung des Reticuloendothels für die Tuberkulosetherapie, Klin Wchnschr, 1930, ix, 822
- 34 SCHURER-WALDHEIM, F Milzbestrahlung und retikulo-endothelialer Apparat, Wien klin Wchnschr, 1930, xliii, 201
- 35 SCHIEFFHAKE, E, and SINCKE, G Über die Wirkung von Milzextrakten auf das reticulo-endotheliale System, Gezeigt an der Trypanblauspeicherung, Klin Wchnschr, 1931, x, 346
- 36 HEROSE, K Experiments in the artificial production of amyloid, Bull Johns Hopkins Hosp, 1918, xlix, 40
- 37 KUCZYNSKI, M H Neue Beiträge zur Lehre vom Amyloid, Klin Wchnschr, 1923, i, 727
- 38 SMETANA, H The relation of the reticulo-endothelial system to the formation of amyloid, Jr Exper Med, 1927, xlv, 619
- 39 JAFFE, R H Amyloidosis produced by injections of proteins, Arch Path and Lab Med, 1926, i, 26
- 40 LETTERER, E Experimentelle Studien über Art und Entstehung des Amyloids, Zentralbl f inn Med, 1926, lvii, 417
- 41 EKLUND, C M, and REIMANN, H A The etiology of amyloid disease, Arch Path, 1936, xxi, 1
- 42 CAVALLACCI, G Osservazioni sull' amiloidosi sperimentale, Pathologica, 1934, xxvi, 303

THE RELATIONSHIP OF AGE TO THE CONCENTRATION OF ACID SOLUBLE PHOSPHORUS IN HUMAN TISSUES¹

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In a preliminary report, Struck and Visscher¹ noted an inverse relation between the ages of two groups of rats and the mean concentration of total acid soluble phosphorus in muscle. Since these two groups were not of homogeneous origin, the work was repeated and extended. A part of the results were embodied in a preliminary report by Bartoli, Cohen and Struck,² confirming the earlier findings.

A survey of the literature on the general subject of chemical changes with aging shows a badly confused state of knowledge.

The fact that the concentration of acid soluble phosphorus of human serum decreases under normal conditions from an average of approximately 5 mg per cent in infancy to 3.5–3.7 mg per cent in the adult has long been known. Similar changes have recently been demonstrated in horses by Pearson³ and in chicks by Elvehjem and Kline⁴. In cattle the concentration of inorganic phosphorus increases slightly from the second to fourth month of life, remaining fairly constant until the tenth month, after which time there is a gradual decline.⁵

Other constituents of blood have also been studied in recent years, and in some cases similar changes have been found to occur. Thus, Currado⁶ has found that the uric acid concentration of the blood of individuals over 70 years of age is definitely lower than that of healthy, young adults. Unfortunately, his data do not include values for infants or children. A change in the copper content of the blood during the first few months of life in humans has been found by Lesne, Zizine, and Briskas.⁷ Apparently there is a fall during intrauterine life, followed by a distinct rise during the first two months of postnatal life. The cholesterol content of human serum has been studied by Eck and Desbordes,⁸ who found that it tends to increase with age, while the cholesterol dissolving power of the blood also increases, the tendency was reversed in individuals over 60 years of age. Kalabukhov and Rodionov⁹ have found that there is a decrease in water content of the blood, together with a decrease in blood acidity and the size of the erythrocytes. The number of cells and the glucose concentration, however, show increases. Kurado¹⁰ has also found this change in water content of the blood of mice.

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Watchorn¹¹ has found that the serum calcium of adult rats is very slightly lower than in young animals, and, while the magnesium content of serum of males also decreases slightly, that of the females remains constant. In the human, however, Kirk, Lewis and Thompson¹² have been unable to find any change in calcium. Glutathione¹³ and plasma lipids¹⁴ have been found to remain constant with respect to age in men. Similarly, no significant changes in urea, non-protein nitrogen, creatinine, uric acid, glucose, sodium, chloride, or ash of chicken blood could be found by Heller and Pursell¹⁵ throughout the life cycle. Certain other constituents were, however, found to change, particularly during the time of egg laying¹⁶.

The chemical composition of tissues other than blood has received some attention, but in very few studies has there been any complete investigation of the composition of the tissues over the entire life span of the species studied. This fact is easily explained by the great difficulties involved in maintaining a large enough colony for a time sufficient to give statistically significant results. Thus most of the results presented in the papers reviewed below are based on data from autopsy specimens, or in nonhomogenous colonies of animals. The possible errors involved in this method are, of course, obvious.

Roche and Leandri¹⁷ report that in the long bones of the rat the phosphatase content is greatest during the period of most active growth, and that, as growth slows and finally ceases, the phosphatase decreases gradually to a constant value. However, no data are presented for extremely old animals. Burns and Henderson¹⁸ have studied the mineral composition of the bones of young pups and kittens, and have found, as was to be expected, that the calcium content rises until growth of the bone is complete. The interesting fact to be noted in their report is that immediately after birth in both pups and kittens there is a short period when the mineral content of the bone decreases. Whether this is a general finding, or may have been due to the particular condition of the experiment, or some other factor, cannot be stated. This point will bear further study.

Blume¹⁹ reports finding that the glycogen content of human hearts is markedly higher in infants than in adults.

Several investigators have studied the variations in enzyme activity of various tissues with the age of the animal. Pearce²⁰ has studied the oxygen consumption of excised liver, kidney, and cardiac tissue from a genetically pure strain of mice at two age periods: 4 to 9 weeks, and at 50 to 60 weeks. He finds significant decreases in all three tissues in the older animals, the greatest decrease occurring in the liver, the least in the kidney. A similar type of study has been made on *Drosophila* by Sekla,²¹ who finds that the esterolytic processes increase from birth to a mean age slightly over maturity, and then decline. Again, Falk and his colleagues²² have found extracts of whole rat show increasing lipase activity from birth to maturity, after which there is a steady drop to the oldest animals studied, three years. This general trend is further confirmed by Lebensohn,²³ who reports that in vitro tis-

sue cultures of old animals show much slower growth rate and carbohydrate utilization than tissues from young animals. The rates are also dependent in the same way, although to a lesser degree, on the age of the animals from which the plasma was obtained for the culture.

The energy metabolism of humans is known to vary with age, there being a definite rise in metabolic rate during prepubertal life, followed by a decline, at first fairly sharp, later more gentle, but continuing throughout life. This same type of variation has been shown by Davis²⁴ to hold for the white rat.

A change in the proportion of liquid and solid fatty acids of subcutaneous tissue has been found by Stolfi²⁷. The subcutaneous tissue becomes richer in oleic acid relative to solid fatty acids as age increases, the change taking place chiefly during early life.

Tung-Pi Chow and Adolph²⁵ have reported analyses on tissues from five cadavers aged three months to "adult," and all tissues examined, except the pancreas, show marked decreases in copper content. Interestingly, Zondek and Karp²⁷ have found that the iron content of cells increases with age in such tissues as liver, kidney, and testis. This increase takes place over a relatively short period of time in the life span and always during the middle or late adult life of the animal. During the remainder of the life span the iron content is constant.

Greenberg and Tufts²⁸ have analyzed the entire carcass of the rat for magnesium and water at various ages, and have found that there is a rapid increase in magnesium from birth to about four weeks of age. The magnesium content remains relatively constant during the next seven to ten weeks, after which time there is a steady decline through the thirtieth month of life. The water content decreases progressively during the 30 month period studied. While these data are of great interest, they do not cover the entire life span of the rat, and, more important, they give no clue as to where the changes take place. A similar type of study has been made by McCay and his colleagues²⁹ in the brook trout. These investigators found that the calcium and phosphorus content of the entire body of the trout show marked increases from one day old (eggs) to 10 months old. Winter³⁰ has found that during the first 31 days of life the total chloride content of the body of the rat decreases about one-third. No data are presented for older animals, however.

Cole and Koch³¹ have studied the phosphorus fractions of striated muscles of rats, and have found that there is a rapid increase in creatine phosphate content from birth to two or three weeks after weaning, a change which may be due to the relatively great increase in exercise during this period. They did not find any significant change after the value had reached its maximum through 168 days of life.

The central nervous system of the rat has been the subject of several studies of this nature. Koch and Koch³² have found that certain definite changes in chemical composition of the brain of the rat occur during the first 210 days of life. The total solids increase about 100 per cent, and in the

solid matter the proteins decrease, while the phosphatids, cerebroside, and sulfatids all show increases. The total sulfur and total phosphorus decrease as well. In the case of the phosphorus, the decrease is due to the protein and water soluble phosphorus, since the lipid phosphorus shows a marked increase over this period. Hatai³³ has analyzed the brains of rats over a 380 day period, and has found that, calculated as per cent of moist tissue, the non-protein nitrogen of the brain remains relatively constant, while showing a definite decrease when calculated as per cent of dry tissue. A more recent study by Epel'baum³⁴ shows that during the first seven days of life the total phosphorus and acid soluble phosphorus of the brain of the rabbit increase markedly, but by 30 days the values have decreased to the adult level.

Max Burger³⁵ has made numerous analyses of various tissues of different species and has found that frequently the curve obtained by plotting the log of the age of the animal against the log of the per cent of the constituent is a straight line. Thus, the per cent of dry residue in human skin and rib cartilage, in cattle lens and cornea, all show increases, although the gradients of the curves are different. The per cent of nitrogen in human skin and rib cartilage, and in cattle lens and skin, likewise are increased. Similar results were found for calcium content of various tissues. Human erythrocytes show definite increase in fragility with age, according to the same author. Studies by Keuenhof³⁶ have shown that the opening of the aorta of the horse shows a marked increase with age, and that the calcium and cholesterol content show approximately 100 per cent increases from 1 to 25 years of age. The cholesterol content of the human aorta shows a marked increase from 1 to 80 years of age.

Moulton³⁷ has studied the water, nitrogen and ash contents of the fat free animals of several species with respect to age of the animal. All curves have the same general form. In general, the water content decreases rapidly to a fairly constant level reached very early in extra-uterine life, the ash and nitrogen content increasing to a constant level reached at the same time as the water content. The author concludes that the animals should be compared on the fat free basis, and on this basis it can be shown that "mammals show a rapid decrease in relative water content, an increase in protein (nitrogen) and ash content from earliest life until the time of chemical maturity is reached. At this time the change becomes rather suddenly less and nearly constant composition is shown. Mammals vary in composition at birth. Those relatively mature have a low water content, and those less mature a high water content." Mammals reach chemical maturity at different ages, but these ages are a fairly constant relative part of the total life cycle, about 4-5 per cent of the cycle being the average.

Bernstein³⁸ has endeavored to express the changes during growth mathematically. He found that certain changes—the increase in cholesterol and insoluble globulin, and the decrease in water—can be correlated to a degree

with the physiological age of the individual, and that those individuals in whom these changes were, for any cause, accelerated tended to die young

Chanutin³⁹ finds that during the period of active growth of the rat the creatine concentration is markedly increased. Fat and ash concentrations reach a maximum at about the twentieth day of life, after which there is a gradual decrease. The nitrogen concentration he finds to be constant throughout life. His analyses, however, do not sufficiently cover the entire adult life of the animal to show changes in creatine content. Chanutin's conclusion regarding nitrogen content may be true in his experiments when whole, eviscerated animals were used. They are, however, in sharp disagreement with various other reports, particularly those of Buiger³⁵ and Hatai³³ who have analyzed individual tissues and report definite variations with age. A more recent report, differing from all these, is that of Asmolv,⁴⁰ who finds that as rabbits grow older the total nitrogen content of hydrolyzed muscle increases while the water content decreases. Hatai⁴¹ has also found this change in water content. His analyses cover less than one year of life, but show that during this time the per cent of solids reaches a maximum while the young are nourished by mother's milk. A more complete study of the water content is that of Lowrey⁴² who has analyzed various tissues of the rat for water during the first year of life. In general, his results indicate that most tissues show a progressive decrease in water content during this interval, the most rapid change taking place during the first four weeks. Lucker⁴³ found a massive increase in the iodine content of the blood of humans over 50 years of age.

Finally, a brief note by Hackh and Westling,⁴⁴ who suggest the possibility that old age may be caused by an accumulation of heavy water in the organism, may be mentioned. There are other papers in the literature on the subject, but they are mostly of the type reviewed here, and are, in general, marred by the same defects. It will be apparent that, while enough information has been gathered to show that some changes do occur during the life of an animal, there is disagreement among various investigators as to just what these changes are. And further, few, if any of the workers have carried out studies over the entire life span of any species. There is, therefore, need for a complete and careful study, particularly of water, nitrogen, and phosphorus, of individual tissues of animals over the entire lifetime from birth to advanced senescence.

The investigations reported herein are concerned wholly with the acid soluble phosphorus content of human tissues. Pectoral muscle, liver and kidney cortex were selected. The material was secured at autopsy. The first intention was to secure fresh material from normal subjects *immediately* after death from accident or suicide. Practical experience, however, soon demonstrated that this was not feasible. Consequently, the question of the extent of postmortem changes came under consideration. Experiments on dogs demonstrated that postmortem changes were confined to the free acid soluble phosphorus but did not affect the total acid soluble phosphorus

In table 1 is shown the distribution of the subjects by age and cause of death. Analysis of any diseased tissue is always open to question. However, a comparison of the data in table 1 with those in table 2 did not show any significant effects of the various disease conditions on the content. It is possible that more data might make possible some such correlation but until additional information is available it is tentatively concluded that none of these pathological conditions significantly affect the content of total acid soluble phosphorus.

TABLE I
Causes of Death

	Prematurity	Accidents, unknown	Diseases of the brain	Diseases of the heart and blood vessels	Diseases of the lungs and respiratory tract	Diseases of the kidney	Diseases of the liver	Diseases of the blood	Carcinomatosis
until 14 da	4				1			1	
until 6 mos					3				
until 3 yrs			1		5			1	
10-13 years			2	1		1		1	
20-30 years		5			1	1			
30-40 years		2	1	1	2	1		1	
40-50 years		2		1	2		1	1	
50-60 years			1	1	2	3			1
60-70 years		3	1	6	2		1		4
over 70 yrs		1	1	3	2				1
Totals	4	13	7	13	20	6	2	5	6

METHOD OF ANALYSIS

The analyses were done by the following method⁴⁵

A sample of tissue (1 to 2 gm) was weighed, ground with sand, placed in a 20 cc graduated centrifuge tube, and water was added. The proteins were precipitated with 5 cc of 20 per cent trichloroacetic acid and the volume made up to 20 cc with water. After shaking and centrifuging, 2 cc of supernatant fluid were drawn off and heated with 0.1 cc concentrated H_2SO_4 . When a dark color appeared 3 drops of 30 per cent H_2O_2 (superioxol) were added. After complete decoloration the excess H_2O_2 was driven off by boiling three minutes with 5 cc of water. The clear solution together with washings was placed in a 25 cc volumetric flask, next 1 cc of molybdic acid solution and 2 cc of hydroquinone solution were added, and the contents mixed. After 5 minutes, 10 cc of Na_2SO_3 - Na_2CO_3 solution were added for the development of the blue color. This mixture was then compared with a standard by colorimeter.

RESULTS

The results of these analyses are shown in table 2. In chart 1 the mean values, as shown in the table, are reduced to graphs which show very definite

trends The values for muscle show a steady increase up to midlife and a steady decline after 40 years of age Because of the wide range of values the data were subjected to statistical analyses by Fisher's formulae¹⁶ and the validity of differences in mean values established Compared to the early figures all values on the ascending limb of the curve are significant and likewise the differences between the apical values and those on the descending slope are significant

The mean values for each sex cannot be interpreted separately since both the proportions and the absolute numbers are too variable in the different groups In the two early groups the means for the females are much lower than for males but the ranges are comparable In the next five age groups

TABLE II

Total Acid-Soluble Phosphorus Mg /100 gm Dried Tissue

Age	Sex	Kidney	Liver	Muscle
<i>Up to 9 days</i>				
1 3 hours	F	40	52	65
2 6 hours	M	44	36	45
3 2 days	M	79	56	61
4 2 days	M	59	71	62
5 3 days	F	58	68	89
6 9 days	M	66	63	78
Mean		58	62	67
Standard deviation		13 58	7 13	13 67
Standard error		5 55	3 19	5 66
<i>Up to 6 months</i>				
7 2 months	M	114	107	89
8 4 months	M	75	83	91
9 6 months	F	69	76	71
Mean		86	89	84
10 6 5 months	F	81	90	84
11 7 months	M	124	135	90
12 7 5 months	F	120	121	—
13 13 months	M	78	67	88
14 15 months	M	82	96	100
15 1 5 years	F	94	128	107
16 3 years	M	120	110	108
Mean		100	113	96
Standard deviation		19 20	16 33	9 35
Standard error		7 26	6 67	3 82
<i>10-13 years</i>				
17 11 years	M	120	103	100
18 12 years	M	78	112	133
19 12 years	M	104	106	93
20 12 years	F	105	116	120
21 13 years	F	103	91	113
Mean		102	106	112
Standard deviation		13 52	8 66	14 22
Standard error		6 05	3 87	6 36

TABLE II (Continued)

Age		Sex	Kidney	Liver	Muscle
<i>20-30 years</i>					
22	20 years	M	122	120	160
23	21 years	M	105	104	126
24	23 years	F	106	115	130
25	28 years	M	98	92	144
26	28 years	M	93	122	145
27	29 years	M	105	95	98
28	30 years	M	96	104	115
Mean			104	107	131
Standard deviation			9 59	10 99	19 19
Standard error			3 92	4 16	7 25
<i>30-40 years</i>					
29	31 years	M	98	106	117
30	31 years	M	—	109	149
31	31 years	M	102	105	128
32	32 years	M	122	109	134
33	34 years	M	100	(136)*	114
34	38 years	F	100	103	145
35	39 years	F	110	124	136
36	40 years	F	89	97	138
Mean			103	108	133
Standard deviation			9 63	7 72	11 60
Standard error			3 64	2 92	4 10
<i>40-50 years</i>					
37	43 years	M	104	107	137
38	43 years	F	78	110	123
39	44 years	F	111	119	124
40	45 years	M	112	127	137
41	46 years	F	126	134	150
42	50 years	M	86	85	89
43	50 years	F	91	109	96
Mean			101	118	134
Standard deviation			15 63	10 30	9 91
Standard error			5 91	4 21	4 43
<i>50-60 years</i>					
44	51 years	M	86	84	90
45	51 years	M	74	88	94
46	53 years	M	102	130	124
47	53 years	F	120	114	122
48	58 years	M	88	92	102
49	59 years	M	76	91	93
50	60 years	F	89	116	—
51	60 years	F	109	110	110
Mean			93	99	105
Standard deviation			15 52	12 50	14 01
Standard error			5 49	4 72	5 29

TABLE II (Continued)

Age		Sex	Kidney	Liver	Muscle
<i>60-70 years</i>					
52	61 years	M	—	79	83
53	61 years	F	89	106	—
54	62 years	F	107	104	121
55	63 years	M	80	125	120
56	64 years	M	85	126	116
57	64 years	M	99	109	117
58	64 years	M	100	82	112
59	65 years	F	99	114	131
60	65 years	M	69	88	74
61	65 years	F	116	124	120
62	65 years	M	56	57	85
63	66 years	M	68	57	100
64	67 years	F	72	88	98
65	67 years	M	68	75	101
66	67 years	M	105	58	91
67	68 years	M	90	100	110
68	68 years	F	76	57	60
Mean			88	91	108
Standard deviation			15 18	24 08	14 00
Standard error			3 92	5 84	3 74
<i>Over 70 years</i>					
69	72 years	M	103	100	102
70	72 years	M	90	90	—
71	73 years	M	70	60	88
72	73 years	M	72	74	67
73	76 years	F	43	69	66
74	85 years	F	71	102	110
75	88 years	M	80	83	92
76	90 years	F	77	87	96
Mean			80	83	89
Standard deviation			11 23	13 79	15 50
Standard error			4 24	4 88	5 86

* Disregarded in calculating standard deviation and error

the means are of the same order. In the last three the means for the males are approximately the same and definitely lower than for the females except in the last group. It is doubtful, however, if any significance can be attached to these differences.

The concentrations of total acid soluble phosphorus in the liver and kidney were of comparable orders with those for muscle up to three years of age. From that time on to 50 years there was no significant change in either. After that age the mean values decreased at about the same rate.

In none of the three tissues were the mean terminal values as low as the initial values. After the six month period the mean values for muscle were consistently higher than for the other tissues, those for the kidney consistently lower.

These results are not entirely in accord with those of another investigation in this laboratory on a colony of white rats. While these results will not be published until later it may be said that no consistent changes in the

content of acid soluble phosphorus were found in any tissue but muscle. In muscle the decrease in concentration began at a period much earlier in the life span than is the case in the human subjects. The reasons for these differences are not clear at present.

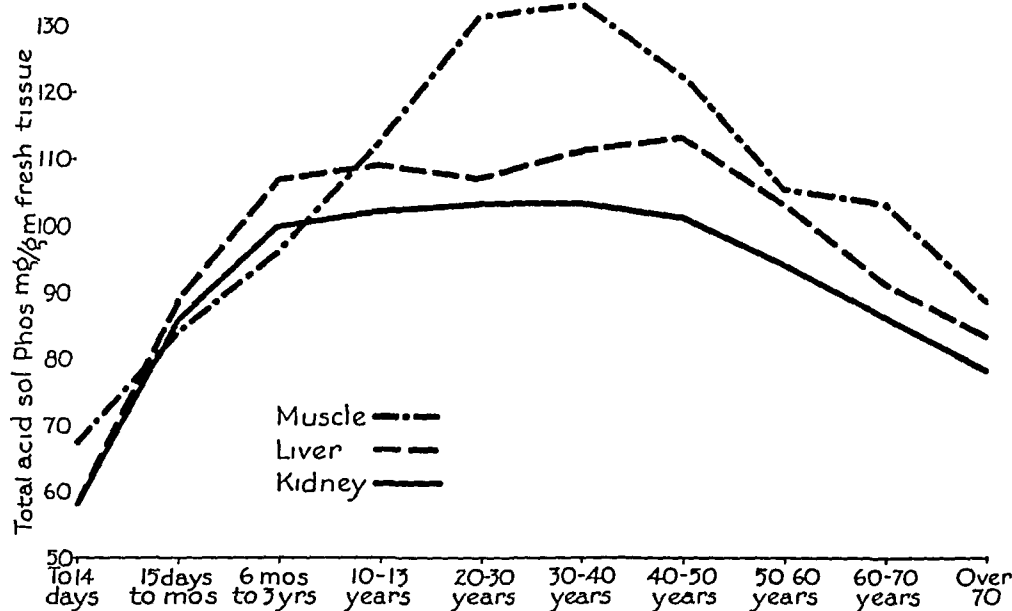


CHART 1

CONCLUSIONS

1 Analyses for the concentration of total acid soluble phosphorus in muscle, kidney and liver tissue from 76 human subjects ranging in age from prematurity to 90 years have been made

2 In muscle the mean concentration increased progressively to 30 years of age and decreased after 40

3 In liver and kidney the mean values increased progressively to three years of age but remained fairly constant thereafter to 50 years, after which there was a progressive decline to 90 years

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BIBLIOGRAPHY

- 1 STRUCK, H C, and VISSCHER, M B. Studies on changes with increasing age in the phosphorus fractions of various tissues of the rat, *Am Jr Physiol (Proc)*, 1935, cxiii, 128
- 2 BARTOLI, A J, COHEN, J L, and STRUCK, H C. A study of the total acid soluble phosphorus in skeletal muscle of rats, *Am Jr Physiol (Proc)*, 1937, cxix, 267
- 3 PEARSON, P B. Inorganic phosphorus of horse serum. Effect of age and nutrition, *Jr Biol Chem*, 1934, cvi, 1

- 4 ELVEHJEM, C A, and KLINE, B E Calcium and phosphorus studies in the chick, Jr Biol Chem, 1933, ciii, 733
- 5 VAN LANDINGHAM, A H, HENDERSON, H O, and BOWLING, G A Composition of the blood of dairy cattle I The effect of age and phosphorus intake on calcium and phosphorus content of cattle whole blood, Jr Dairy Sci, 1935, xviii, 557
- 6 CURRADO, C L'Uricemia nell'et  senile, Boll Soc ital biol spec, 1929, iv, 9
- 7 LESNE, E, ZIZINE, P, and BRISKAS, S B Note sur les variations du cuivre dans le differents ages, Compt rend Soc biol, 1936, cxvi, 1582
- 8 ECK, M, and DESBORDES, J Influence de l'age sur les variations de la cholesterinemie et du pouvoir cholesterolytique, Compt rend Soc biol, 1935, cxviii, 498
- 9 KALABUKHOV, N, and RODIONOV, V Changes in the blood of animals according to age Changes in the blood of rodents (*Mus musculus* L and *Citellus pygmaeus* Pall) and birds (*Passer montanus* L and *Larus ribibundus* L) during the period of growth, Folia Haematol, 1934, lii, 145
- 10 KURADO, K  tudes sur la teneur en eau dans le sang de la souris au cours du developpement, Keijo Jr Med, 1934, v, 140
- 11 WATCHORN, E Normal serum calcium and magnesium of the rat Relation to sex and age, Biochem Jr, 1933, xxvii, 1875
- 12 KIRK, E W, LEWIS, W H, and THOMPSON, W R The effect of age on plasma calcium content of men, Jr Biol Chem, 1935, cvi, 641
- 13 PARAF, J La glutathionemie et la senilite, Ann d Med, 1935, xxxviii, 219
- 14 PAGE, I H, KIRK, E, LEWIS, W H, JR, THOMPSON, W R, and VAN SLAKE, D D Plasma lipids of normal men at different ages, Jr Biol Chem, 1935, cvi, 613
- 15 HELLER, V G, and PURSELL, L Chemical composition of the blood of the hen during its life cycle, Jr Biol Chem, 1937, cxviii, 549
- 16 HELLER, V G, PAUL, H, and THOMPSON, R B Changes in blood calcium and phosphorus partition during the life cycle of the chicken, Jr Biol Chem, 1934, cvi, 357
- 17 ROCHE, J, and LEANDRI, A  tude quantitative de la phosphatase des os longs au cours de la croissance du rat, Compt rendu Soc biol, 1935, cxix, 1141
- 18 BURNS, C M, and HENDERSON, N The mineral constituents of bone II The influence of age on the mineral constituents of bones from kittens and pups, Biochem Jr, 1936, xxx, 1207
- 19 BLUME, H Chemische Untersuchungen  ber den Glvkogengehalt und Gesamtkohlhydratgehalt des menschlichen Herzens, Beitr z path Anat, 1934, xciii, 20
- 20 PEARCE, J M Age and tissue respiration, Am Jr Physiol, 1936, cxiv, 255
- 21 SEKLA, B Esterolytic processes and duration of life of *Drosophila melanogaster*, Brit Jr Exper Biol, 1938, vi, 161
- 22 FALK, K G, NOYES, H M, and SUGIURA, K Lipase actions of extracts of the whole rat at different ages, Jr Gen Physiol, 1925, viii, 75
- 23 LEBENSOHN, E G Beziehungen zwischen Alter, Zellstoffwechsel und Wachstumsgeschwindigkeit in vitro, Arch exper Zellforschung, 1934, xxi, 364
- 24 DAVIS, J E Effect of advancing age on the oxygen consumption of rats, Am Jr Physiol, 1937, cxix, 28
- 25 STOLFI, G Ricerche sulla costituzione chimica del grasso del connattivosottocutanea dell'uomo I Acidi grassi liquidi e solidi nei vari periodi della vita, Boll soc ital Biol spec, 1935, x, 108
- 26 TUNG-PI CHOW, and ADOLPH, W H Copper metabolism in man, Biochem Jr, 1935, xxix, 476
- 27 ZONDEK, S G, and KARP, J The relationship of iron with the ageing of cells, Biochem Jr, 1934, xxviii, 587
- 28 GREENBERG, D M, and TUFTS, E V Variations in magnesium content of the normal white rat with growth and development, Jr Biol Chem, 1936, cxiv, 135
- 29 MCCAY, C M, TUNISON, A V, CROWELL, M, and PAUL, H The calcium and phos-

- phorus content of the body of the brook trout in relation to age, growth, and food, Jr Biol Chem, 1936, cxiv, 259
- 30 WINTER, K A Der Gesamtchloridgehalt neugeborener Ratten, Biochem Ztschr, 1934, cclxii, 384
 - 31 COLE, V V, and KOCH, F C A study on the phosphorus distribution in rat striated muscle as influenced by age, diet, and irradiated ergosterol, Jr Biol Chem, 1931, xciv, 263
 - 32 KOCH, W, and KOCH, M L The chemical differentiation of the brain of the albino rat during growth, Jr Biol Chem, 1913, xv, 423
 - 33 HATAI, S Amount of non-protein nitrogen in the central nervous system of the normal albino rat, Jr Comp Neur, 1917, xxviii, 361
 - 34 EPEL'BAUM, S E, KHAIKINA, B I, and SKVIRSKAYA, E B Effect of age on phosphorus compounds of the brain, Ukrain Biokhem Zhur, 1936, ix, 613
 - 35 BURGER, M Die chemischen Altersveränderungen im Organismus und das Problem ihrer normalen Beeinflussbarkeit, Verhandl d deutsch Gesell f inn Med, 1934, xlv, 314
 - 36 KEUENHOR Quoted by Burger ³⁵
 - 37 MOULTON, C R Age and chemical development in mammals, Jr Biol Chem, 1923, lvii, 79
 - 38 BERNSTEIN, FELIX Growth and decay, Cold Spring Harbor Symposia, 1934, ii, 209
 - 39 CHANUTIN, A The influence of growth on a number of constituents of the white rat, Jr Biol Chem, 1931, xciii, 31
 - 40 ASMOLOV, E Variations in nitrogen fractions and water content of rabbit muscles at different stages of growth, Bull biol med, U S S R, 1936, i, 119, 121
 - 41 HATAI, S Changes in the composition of the entire body of the albino rat during the life span, Am Jr Anat, 1917, xxi, 23
 - 42 LOWREY, G L The growth of the dry substance in the albino rat, Anat Rec, 1913, vii, 143
 - 43 LUCKER, H Kritik der Blutjodbestimmungs-methoden bei alkalischer und saurer Verbrennung, Deutsch Arch f klin Med, 1933, clxxv, 681
 - 44 HACKH, I W D, and WESTLING, E H A possible cause of old age, Science, 1934, lxxix, 231
 - 45 PINCUSSEN, L Mikromethodik, 155, 6th ed, 1937
 - 46 FISCHER, R H Statistical methods for research workers, 1928

INFARCTION OF THE HEART. III. CLINICAL COURSE AND MORPHOLOGICAL FINDINGS¹

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IN the first two parts of this study the underlying conditions predisposing to cardiac infarction, and the symptomatology of acute attacks were presented. In this paper the course, common sequelae and morphological data will be discussed.

CLINICAL FEATURES AND COMPLICATIONS FOLLOWING INFARCTION

Congestive Failure The very important part played by congestive failure after coronary thrombosis has been studied carefully by Master and his associates.²⁰ Evidence of "backward" failure appeared in the form of ankle edema in 55 per cent of these cases. In some it had been present before. In others death occurred before much failure developed. *Enlargement of the liver*, at times with ascites, was observed in 20 per cent of the small number of cases with data on this point. It was found relatively more frequently when the right ventricle was badly damaged, as noted by Libman,²¹ but also in cases where the left ventricle was the only part involved morphologically. *Jaundice* was found 11 times. In two cases an associated "alcoholic" cirrhosis, and in one case a stone in the ampulla of Vater were found. In the remainder passive congestion was present. Three had so-called "cardiac cirrhosis." In six cases infarcts of the lung were present. No patient survived an attack associated with jaundice.

Shock A combination of the varied peripheral and central phenomena comprising the clinical picture of shock appeared in more than half of the cases. In others, though present, it was overshadowed by manifestations of congestive failure. It was often severe when pain was marked, but each appeared alone in some cases. The so-called characteristic facies of acute infarction is largely descriptive of clinical shock.

Extracardiac Embolism and Infarction Embolism from dislodged mural thrombi is one of the unpredictable complications of cardiac infarction which makes prognosis doubtful. In table 1 are presented the data for embolism and infarction and the time after cardiac infarction at which embolism appeared. Careful study failed to reveal any clue by which it could be predicted that embolism would occur. No association was found with age, sex, blood pressure level, pain, use of digitalis or other factors. Approximately one-half of those with auricular fibrillation had mural throm-

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TABLE I
Peripheral Embolism and Infarction After Cardiac Infarction

Location	Embolus Derived From Mural Thrombus	Embolus Derived From Non-Cardiac Site	Infarct Without Local Arterial Damage or Mural Thrombus	Infarct Derived From Local Arterial Disease	Total
Lung	19	9 (Leg 3, Pelvis 1, ? 5)	15 (10 recent)		43
Kidney	20	2 (Bacterial endocarditis)	4 (old)	3	29
Spleen	13	1 (Aortic mural thrombus)	3 (old)		17
Brain	6			9(2 hemorrhage)	15
Femoral	5			3	8
Mesenteric	2			1	3
Carotid	1				1
	66	12	22	16	116

Embolism occurred 78 times in 60 cases

Time of Embolism After Cardiac Infarct

	Day													Week		Month		Total	Un- Known
	4	5	6	7	8	9	10	11	12	13	14	3	4	2	3				
Number of Cases	1			3	2	2	1	2	2	1	2	6	9	2	3	36	30		

bosis, but it did not predispose unduly to dislodgment and embolism. It was found that embolism of cardiac origin was not usually fatal unless to the leg, brain or mesentery. Emboli from the right side of the heart were frequently present, but massive embolus occluding the lumen of the pulmonary artery was always derived from systemic veins. Pulmonary infarcts were most frequent in the lower lobes.

In this series cerebral vascular accidents following cardiac infarction were more frequently thrombotic, depending on local vascular fault, than embolic. It may be that the rapid fall in arterial tension after injury to the heart was enough to cause formation of a thrombus where disease was already present in the artery.

There were 15 cases of pulmonary infarction without any thrombus or embolus in the pulmonary arterial tree. These cases were invariably associated with marked left ventricular failure, stasis in the pulmonary circuit and pulmonary venous thrombosis. Such examples of cerebral and pulmonary infarction indicate that local vascular disturbances following cardiac infarction are responsible for a proportion of clinical phenomena which are often assumed to be embolic in nature. In addition, these findings might be taken to support the belief of an increased thrombotic tendency of the blood in coronary thrombosis. The earliest embolic accident occurred on the

fourth day after the acute cardiac lesion, but the majority appeared in the second, third and fourth weeks. A few cases met with the accident months after infarction.

PROGNOSIS

The likelihood of survival in any case of cardiac infarction depends on many different factors and unpredictable complications. Data on survival are recorded in table 2. Until a method is devised to forecast embolism,

TABLE II
Survival After Initial Attack

	Weeks						Months						Years							
	1	2	3	4	5	6	2	3	4	5	6	8	10	1	2	3	4	5	6	old
Number of Cases Dying Before End of Period Indicated	45	37	10	12	4	6	5	10	6	4	11	12	4	15	11	14	6	5	3	80

Survival After Acute Attack

Number of Cases Dying Before the End of Period Indicated	Days														Weeks			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	3	4	5	6
(114) First infarct	12	9	5	5	5	5	6	5	5	2	7	6	5	7	10	12	4	6
(67) Second infarct	10	3	4	4	5	3	7	1	4	2	2	1	2	3	7	4	2	3
Total	22	12	9	9	9	7	13	6	9	4	9	7	7	10	17	16	6	9

rupture and syncopal deaths, prognosis must rest on probability. If we assume the absence of complications, then indications of a large infarction are of grave significance. Clinically these are signs of either severe shock or congestive failure or both—namely, large heart, tachycardia, edema, both pulmonary and peripheral. Of the laboratory findings in uncomplicated cases a high fever, high leukocytosis with a shift to the non-filamented cells, rapid sedimentation rate, high non-protein nitrogen usually indicate a large area of damage. Electrocardiographic evidence of irregularities of rhythm and conduction defects is of more value prognostically than is the degree of T-wave change for this latter is not necessarily proportional to the damage to the heart. Pulmonary infarction or pneumonia adds to the gravity of the condition but are not necessarily fatal. Cases may end in recovery or death, quite contrary to all prognostic indications. The criteria of prognosis stressed in the literature are statistically valuable and show definite trends for groups of cases. Prognosis is the art of predicting the outcome of an *individual* case, however, and as yet no method or combination of methods exists by which accurate prophesy of final results can be made early in individual cases of infarction.

CAUSE OF DEATH

Seasonal variation in death rate for different conditions is a well-established fact. Figure 1 shows the relationship of acute attacks and deaths by season*. There is a constant increase from the low summer death rate through fall to the high winter and spring rates. In addition to the factors which govern seasonal changes in death rate from congestive failure and related conditions, a very important factor in this series is the

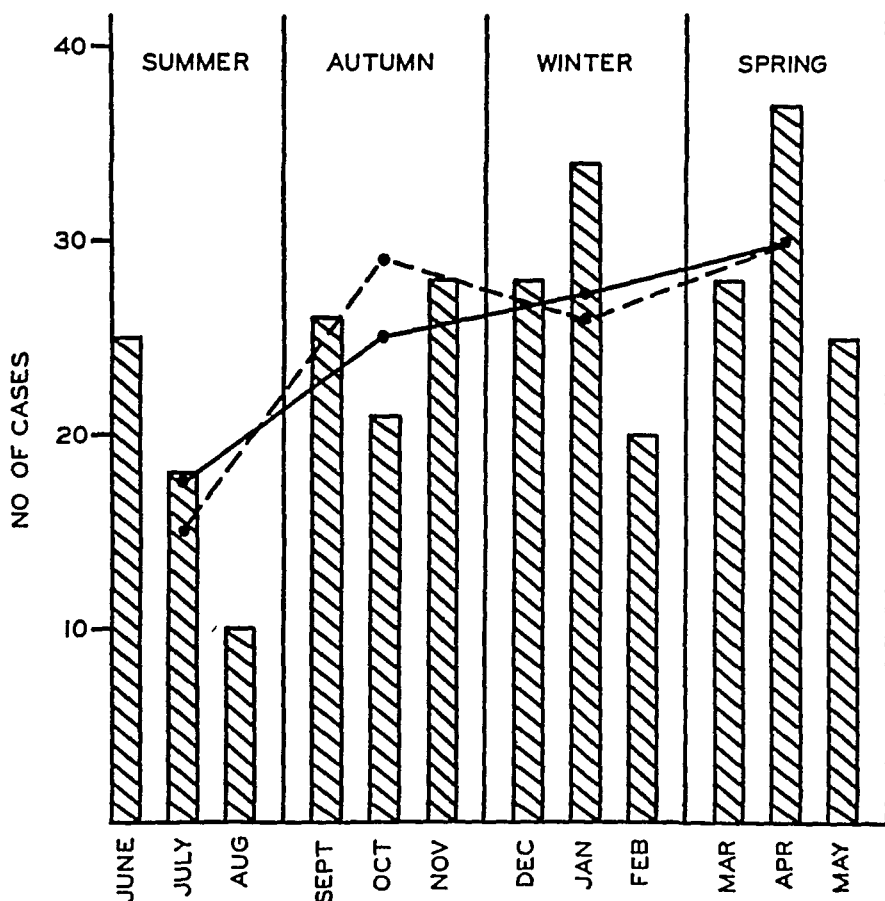


FIG 1 Distribution of deaths by month and season. The unbroken line represents the percentage of deaths (300), the broken line represents the percentage of acute attacks (247) in each season.

seasonal difference in frequency of acute attacks. Since 166 cases died within a month of the acute episode, the seasonal incidence of deaths shows a close relation to the distribution of acute attacks.

Age at death for the whole group averaged only one year older than age at onset for those where date of onset was known. The charted distribution by decades superimposes almost exactly that for age at onset (see Part I). Because the survival period was unknown in so many cases with obviously old scars, the data for duration of life after infarction are incomplete and not accurate.

* For acute attacks by month see Part I, *Am Heart Jr*, 1937, xiv, 684.

In table 3 are found the number of cases in which varied factors were the main or contributory *causes of death* in the groups of infarcts studied. The prime cause of death in this series was congestive failure, a point recently stressed by Master²⁶ and others. The next most frequent cause of death was collapse and shock. The mechanism of death in such cases of "dyskinetic" and "hypokinetic" cardiac failure has been admirably expounded by Harrison¹².

Under the head of syncope are included all cases of instantaneous death where the victim literally dropped dead or died unexpectedly with symptoms lasting too short a time for any observations to be made. In addition, five cases found dead in bed were probably similar. No case with embolism had such a death, nor was there any case where death followed coronary thrombosis in less than one hour and a quarter. Unpredictable sudden death has long been known as a frequent associate of angina pectoris and coronary thrombosis. The mechanism has been explained variously by Allbutt as due to vagal inhibition and ventricular standstill, by Hering as ventricular fibrillation, by Leary as "coronary spasm" and by Levy as "acute fatal coronary insufficiency" without spasm. Each of the above speculations apparently assumes that the cause of death is something which, interfering with the cardiac mechanism, effects a condition of actual or functional asystole. It would be expected that ensuing manifestations would be those of cerebral anoxemia, particularly respiratory effort and such changes as occur in the asystolic phase of an Adams-Stokes' attack. From the meager information available it is found that in the instant deaths in this series there was a total cessation of "vital" functions as a precipitously occurring syncope, irrevocable in nature.

In a study of syncope Weiss¹³ has suggested that the tendency to fainting may become enhanced as a conditioned reflex. In addition, he has demonstrated that fainting and convulsions may be produced in one form of carotid sinus syncope without the intermediation of cardiac or depressor reflexes, being a purely cerebral reflex.¹² With these points in mind a careful study of the past history and clinical course of these cases was undertaken. Seventeen of the 29 cases of sudden death had a history of some form of fainting or syncopal attacks prior to infarction. The group with syncope had a greater liability to sudden death than the groups with angina pectoris, hypertension, congestive failure or the various types of conduction defects. On the basis of these facts we wish to emphasize the abrupt and apparently simultaneous cessation of the functions of heart beat, respiration and consciousness as a "totalitarian" form of death frequent after cardiac infarction, cerebral in origin, evidently depending on reflexes from the damaged heart, rather than asystole per se.

There were cases without embolism or rupture where the heart beat was undetectable clinically and death followed minutes after the first sign of air hunger, intense respiratory effort and cyanosis, usually with some convulsive

TABLE III
Cause of Death

	Old Cases		Old and Recent		Recent		Total		Total
	Main	Con-tributory	Main	Con-tributory	Main	Con-tributory	Main	Con-tributory	
Cardiac									
Congestive failure	52	18	25	40	28	50	105	108	213
Pulmonary edema	3	46	2	48	4	61	9	(155)	(164)
Cardiac cachexia	5	4	1			1	6	(5)	11
Rheumatic heart disease	2	4		2	1		3	(6)	9
Bacterial endocarditis		1				4		5	5
Paroxysmal tachycardia				2		2		4	4
Digitalis poisoning		1				1		2	2
Total	62		28		33		123	119	242
Shock									
Collapse and shock		13	12	14	32	23	44	50	94
Syncope, sudden death	5		12	2	12	3	29	5	34
Rupture			4*		14		18		18
Total	5		28		58		91	55	146
Vascular									
Embolism	9	12	6	21	6	24	21	57	78
Cerebral vascular accident	11	9	3	1	3	2	17	12	29
Gangrene of leg	3	3			1	1	4	4	8
Mesenteric thrombus	1			(1)†	(1)†		1(1)	(1)	(2)1
Total	24		9		10		43		116
Infection									
Bronchopneumonia	2	22		7		17	2	46	48
Syphilitic aortitis		3		2		5		10	10
Lobar pneumonia	4		1	2			5	2	7
Empyema	1	1	1	1	1	2	3	4	7
Sepsis		4				3		7	7
Cholecystitis		3		3		1		7	7
Tuberculosis	2	1		1			2	2	4
Urinary tract infection		1		1		2		4	4
Erysipelas	1						1		1
Peritonitis			1				1		1
Purulent pericarditis			1				1		1
Total	10		4		1		15		91

* 1 Traumatic

† Embolus

TABLE III—Continued

	Old Cases		Old and Recent		Recent		Total		Total
	Main	Contributory	Main	Contributory	Main	Contributory	Main	Contributory	
Miscellaneous									
Diabetes	2	3	1	4	5	4	8	11	19
Operations	3	1	3		5	1	11	2	13
Uremia	3	2		3		2	3	7	10
Peptic ulcer		4	1	2	1	2	2†	8	10
Trauma		1	1	1		1	1	3	4
Hemorrhage				1		2		3	3
Carcinoma	1	2					1	2	3
Alcoholic cirrhosis		2		1				3	3
Hodgkin's disease	1						1		1
Lymphoid leukemia					1		1		1
Hemochromatosis		1						1	1
Partial coarctation of the aorta						1		1	1
Total	10		6		12		28		

† Rupture

movements. Apparently these cases were *primarily* due to some form of cardiac standstill.

Embolism was the direct cause of death in 21 cases and contributed in many more. The only cases where it was rapidly fatal were those with massive pulmonary embolus from a systemic vein. All of these survived for at least ten minutes, and many for hours after the first symptom.

Many other factors listed in the table are self-explanatory in their rôle as lethal agents.

MORPHOLOGICAL CONSIDERATIONS

The fundamental principles of the structural changes in cardiac infarction have been understood since they were enunciated by Weigert⁴¹ and Ziegler⁴⁶. Certain obscure points still exist, and others are found which may be elucidated by statistical presentation.

Location of Arterial Damage and Infarction. There is still some disagreement in the literature regarding the prevalence of involvement of different arteries. The early reports of Wearn⁴⁰ and Levine¹⁷ revealed a great preponderance of lesions of the left anterior descending artery. In subsequent studies Parkinson and Bedford³² and Barnes and Ball³ have found a different distribution, and the latter writers concluded that designation of the left anterior descending branch as "*the* artery of coronary occlusion" was no longer justifiable. Some of the reported groups have

TABLE IV
Arterial Distribution

Author	Left Anterior Descending	Right Main	Left Circumflex	Left Main	Miscellaneous	Total Lesions	Number of Cases
This series	242	60	55	13		370	287
Appelbaum and Nicolson	85	29	8	7	16	145	113
Parkinson and Bedford	24	18	10	3		55	55
Barnes and Ball	28	20	17			65	49
Levine	39	2	4		1	46	46
Lisa and Ring	22	4	1			27	24
Wearn	16	1	1		1	19	19
	456 (77%)	134 (23%)	96 (16%)	23 (4%)	18 (3%)	727	593

been tabulated and compared with this series in table 4. In the combined groups more than 75 per cent of all cases had a lesion of this artery and, in this series, 84 per cent of cases. Furthermore, as table 5 shows, the right coronary tree was involved seriously in only 21 per cent of the 287 cases.

TABLE V
Distribution of Arterial Lesions
Artery

Left anterior descending chief lesion	178
Right main	16
Left circumflex	14
Left anterior descending and left circumflex	12
Left main	10
Left main and right main	8
Left anterior descending narrow right main thrombosed	8
Right main and left circumflex	7
Left anterior descending narrow, left, circumflex thrombosed	5
" " " thrombosed, right main narrow	5
" " " " and left circumflex narrow	4
" " " left circumflex narrow	4
" " " narrow, right main narrow and left circumflex narrow	3
Right main and left circumflex	3
Left main and left anterior descending	2
Right main and left main narrow	2
Right descending, left anterior descending and left circumflex narrow, right and left main and left circumflex	
Left anterior descending narrow, right main and right descending thrombosed, intraventricular branch of left anterior descending, right main and anterior descending thrombosed and left circumflex narrow—1 each	6
	287
Left anterior descending	242
Left circumflex	55
Left main	13
Right main	56
Right descending	4
Left coronary tree	270
No artery	5
Right coronary tree	60
?	8

This information substantiates the impression that the left coronary artery, particularly its anterior descending branch, is the most prominently involved artery in infarction. A cause for this peculiar liability has been advanced by Lewis¹⁹ as due to "the relatively more exposed position" of the artery.

Whitten ⁴⁴ demonstrated that muscular branches supplying the left ventricle leave the parent stem at right angles to enter the muscle directly. This anchoring is said to cause buckling of the main artery between fixed points, favoring local damage. One might, therefore, expect more frequent damage to the left circumflex artery than is known to occur.

In the great majority of cases there was involvement of more than one artery or branch in the damaging changes leading to infarction. This is in general agreement with Saphir and his coworkers' observation of multiple lesions in the artery in every case in their study. There were some notable exceptions. In eleven cases there was no damage at all in the right coronary artery but only in the anterior descending branch of the left coronary, and in one case two infarcts had occurred with only this artery involved. Examples of isolated damage to the left circumflex or right main artery also appeared, but these cases were in the minority.

There was fairly close agreement between artery involvement and the location of myocardial infarction. Table 6 gives the distribution of gross

TABLE VI
Site of Infarct

	Single	Multiple	Total
Anterior apical region of left ventricle, right ventricle little involved	91	30	121
Anterior apical region of both ventricles and intraventricular septum	51	26	77
Posterior basal region of left ventricle	20		20
Anterior basal region of left ventricle	7	6	13
Lateral region of left ventricle	9		9
Lateral and posterior region of left ventricle	7	2	9
Anterior region of right ventricle	6	2	8
Anterior and lateral region of left ventricle and septum		7	7
Posterior apical region of left ventricle	5	1	6
Anterior and posterior region of left ventricle and septum		5	5
Posterior basal region of left and right ventricle and septum	2	3	5
Anterior and lateral region of left ventricle	1	1	2
Anterior and lateral and posterior region of left ventricle	1	1	2
Anterior and post-apical region of left ventricle and posterior base of left ventricle		2	2
Anterior basal region of right ventricle	1		1
Anterior basal region of left ventricle and all of right ventricle		1	1
Anterior apical region of left ventricle and lateral aspect of rt vent		1	1
Anterior apical region of left ventricle and anterior aspect of rt vent		1	1
Anterior apical region of left ventricle and anterior basal aspect of left ventricle		1	1
Papillary muscles alone	2		2
Papillary muscles and anterior apical region of left ventricle	2		2
Papillary muscles and posterior basal region of left ventricle	2		2
Papillary muscles and posterior basal region of right ventricle	1		1
Papillary muscles and anterior apical region of right ventricle	1		1
Papillary muscles and posterior basal region of left ventricle and lateral aspect of left ventricle	1		1

Left ventricle involved in 287 cases
 Septum 111
 Right ventricle 95
 Papillary muscles 10
 Auricle 3

TABLE VII
Location of Infarct

Author	Anterior and Apical Portion of Left Ventricle	Lateral Region of Left Ventricle	Posterior Basal Region of Left Ventricle	Right Ventricle	Miscellaneous	Total
This series	223	30	43	9	25	300*
Appelbaum and Nicolson	91	10	16	0	10	118
Barnes and Bell	28	8	24	0	3	63
	342 (71%)	48 (10%)	83 (17%)	9 (2%)	38 (8%)	481

* Many of the cases with multiple infarcts in this series had both infarcts in the same general location

lesions as described in the protocols. In a few cases the location was atypical, but the larger number of cases fell into one of the three groups illustrated by MacCallum²¹. In 72 per cent of all cases the lesion was located in the anterior apical part of the left ventricle, frequently with some involvement of the right ventricle and septum.

Recently Saphin and his coworkers³⁵ have reported observations on carefully dissected hearts with coronary artery lesions, citing some cases where a fresh infarct was not in the area supplied by a recently thrombosed artery. The infarct was in the region normally supplied by a previously obstructed artery, but the collateral supply had been taken over by the branch whose final obstruction resulted in a kind of "ectopic" infarction. There were nine cases in this series which can be explained on this basis (see table 8).

TABLE VIII
Infarcts Not in Area of Recent Thrombus

Fresh thrombus of left anterior descending, old occlusion of right main and infarct chiefly posterior and in right ventricle	3
Fresh thrombus of left anterior descending, narrow left circumflex, fresh infarct in lateral area of left ventricle	1
Anterior apex left ventricle, old scar and fresh thrombus in recanalized left anterior descending, old occlusion of left circumflex, fresh infarct in lateral and posterior left ventricle	1
Left circumflex fresh thrombus, infarct in anterior apex of left ventricle with narrow left anterior descending	1
Right coronary fresh thrombus, infarct in anterior apex of left ventricle especially system where left anterior descending is narrow	1
Old thrombus of left anterior descending, right main narrow, old scar at base posteriorly chiefly in area of supply of right main	1
Left anterior descending narrow, old scar in area, and fresh thrombus. Right main complete old occlusion. Left circumflex narrow, fresh infarct lateral left ventricle	1

Coronary occlusion or thrombosis and myocardial infarction are not identical and they do not follow invariably as cause and effect. Either may occur without the other. It is probable that the process of infarction differs in occlusive and constrictive arterial lesions. Table 9 gives the cases where

TABLE IX

Location of Infarcts Without Complete Occlusion of Artery

<i>Left anterior descending narrow—no occlusion</i>	
Old scar anteriorly and apex of left ventricle	32
Fresh infarct anteriorly and apex of left ventricle	15
Old scars with evidence of recanalization	8
Old scar and recent infarct anterior apex of left ventricle	1
<i>Left anterior descending narrow, right main narrow</i>	
Old scar anterior apex of left ventricle	1
Fresh infarct anterior apex of left ventricle	1
Old scar anterior apex of left ventricle and fresh posterior basal of left ventricle	1
<i>All arteries sclerotic and narrow</i>	
Posterior base of left ventricle and septum, old	3
Posterior base of left ventricle and septum, recent	1
Anterior right and left ventricle and septum—old and recent infarct	1
Anterior apex of left ventricle, posterior basal of left ventricle	1
<i>Left circumflex narrow</i>	
Two old scars in lateral wall of left ventricle	1
Number of infarcts and scars without complete occlusion	58

infarction occurred without a complete obstruction in the artery but where fibrotic narrowing, calcification, atheromatous abscesses or partial thrombosis produced permanent decrease in caliber of the artery. Approximately 20 per cent of the infarcts in this series were of this type. In these cases a careful search had been made for thrombosis of the artery leading to the infarct and none was found.

In some of these cases it is probable that myocardial damage followed *pari passu* the gradual narrowing of the arterial lumen as a so-called chronic infarct developed. Some of the silent infarcts were of this type. There were cases of acute infarction, however, easily recognized clinically as typical "coronary thrombosis," where myocardial infarction had occurred without any acute morphological change in the artery. Spasm was structurally impossible in these calcified and constricted coronaries. The pathogenesis of this type of infarct is unknown. No systematic study has been made of the coronary veins in these cases. In many individuals congestive failure was marked. It is recognized that coronary venous thrombosis may cause a clinical picture characteristic of coronary artery thrombosis³¹ with morphological changes in the heart, while in other cases the heart may show no damage.³⁰ The suggestion is made that a combination of decreased arterial supply plus the increased venous pressure and stasis in the coronary veins, with or without venous thrombosis, may result in characteristic morphological infarction.

Of the five cases with normal arteries and no thrombus or embolus, one was an example of syphilitic occlusion of the mouth of a coronary artery. One was an infarct of a hypertrophied papillary muscle in an enlarged heart with mitral stenosis of rheumatic origin. In two cases perfectly normal arteries led to an infarct in the anterior apical region of the left ventricle.

There was one case of an old aneurysm with extensive adhesions and calcium in the scar but normal arteries were found. In the last four cases diligent search revealed no cause in the arteries for the myocardial lesions found. That coronary spasm may be sustained long enough to result in infarct is conceivable, but again the possibility of venous stasis and thrombosis seems a preferable speculation.

Coronary Anomalies A few cases in this series had unusually located arteries with arteriosclerotic lesions and thrombosis. These are outlined in table 10. In all cases where an artery was abnormally placed structural changes had occurred.

TABLE X

Coronary Anomalies

Right coronary double with occlusion of branch which supplies anterior right and left ventricles and septum instead of normal left anterior descending	2
Division of left anterior descending into a right and left branch at its origin	
Old infarct at base, fresh infarct at apex, anterior, old thrombus in right branch, fresh in left	2
Old infarct at base in anterior part of left ventricle, and occlusion of right branch	1
Infarct at apex of left ventricle and occlusion of left branch	1
Aneurysm of left branch and thrombus with infarct at anterior and apex of left ventricle	1
Anomalous course of left circumflex with occlusion	1
(Partial coarctation of aorta—1 case)	

In one of the cases where the left anterior descending branch was double, a small (5 to 6 mm) aneurysm of the coronary artery was the site of thrombosis and infarct. There was microscopic evidence of degenerative changes in the artery but no evidence that the nature of the process was mycotic.

Heart Weight Cardiac hypertrophy is frequently associated with hypertension, angina pectoris and congestive failure, as well as symptomless coronary disease. The literature stresses enlargement of the heart in cases of thrombosis^{40, 17, 32} (figure 2). In addition, Bartels and Smith⁴ have alleged coronary thrombosis as a cause of hypertrophy without these other factors. In this series it was impossible to find many cases in which one factor alone was present. Table 11 gives the average weights of hearts in different categories. Using 350 and 400 grams as the upper limit of normal

TABLE XI

Heart Weight

Number	Range grams	Average grams
Men (205)	280-830	531
Women (90)	260-720	468
Hypertensives (137)	290-830	542
Hypertension not demonstrated (158)	260-800	480
Failure, no hypertension (25)	280-800	436
No failure or hypertension (8)	280-540	414
Total 295	260-830	512

for hearts in women and men, respectively, it was found that 83 per cent of women and 83.4 per cent of men had hearts heavier than normal.

The known hypertensives had hearts averaging 62 grams heavier than the rest of the cases. In the eight cases where no hypertension or failure had been present the average heart weight was only 414 grams, but two of

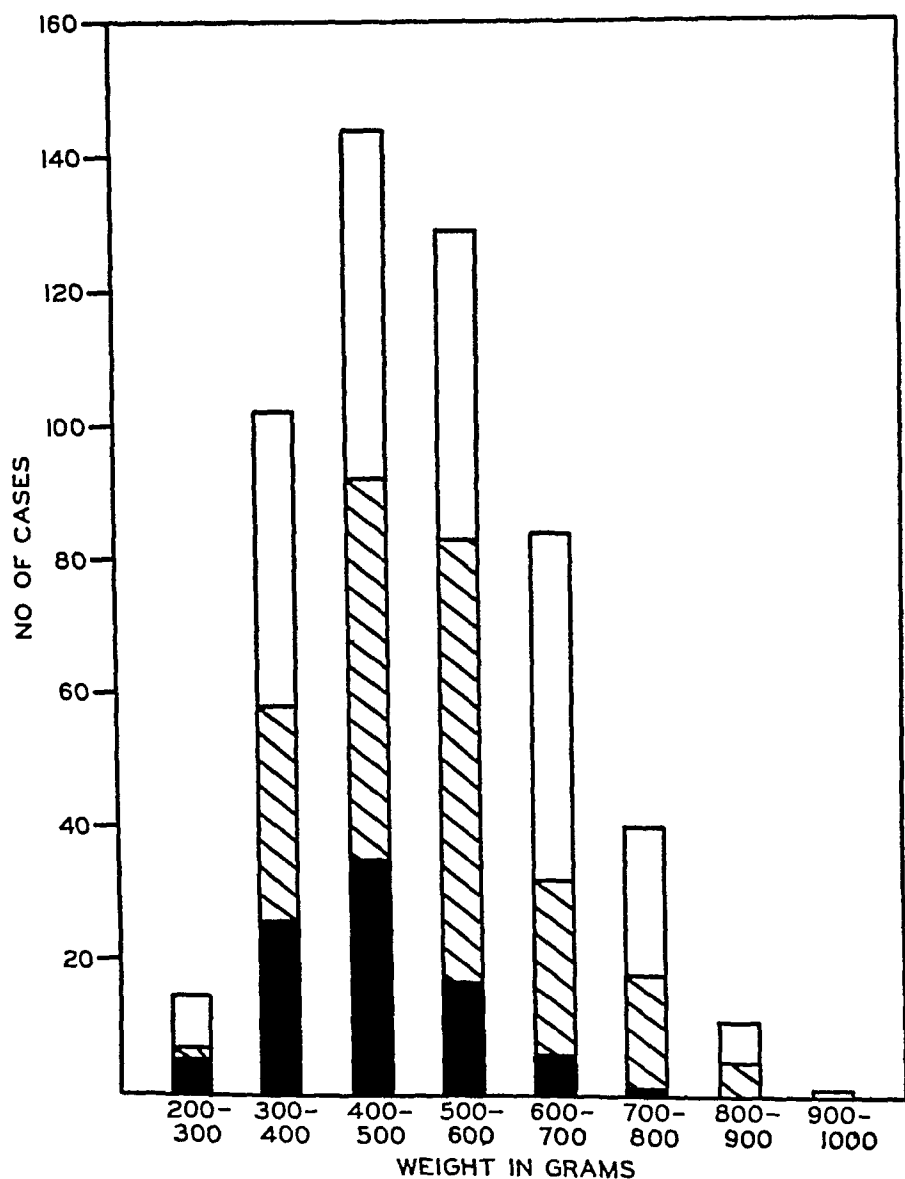


FIG 2 Heart weight. Solid represents females, cross-hatched represents males in this series. The unmarked groups are additional cases from the literature.

these weighed more than 500 grams. Clinical evidence that the post-infarction heart may not be enlarged is found in Palmer's report²⁹ that 36 per cent of cases surviving three months or more did not have clinically detectable enlargement. The conclusion seems justified that the majority of cases dying with cardiac infarction have enlarged hearts.

Intracardiac Mural Thrombi Corvisart¹⁰ was one of the first to note the occurrence of intraventricular mural thrombi, but their significance was not comprehended until the pathology of infarction was better known. Reports of the incidence of mural thrombosis after infarction give widely divergent figures. For example, Parkinson and Bedford found only 14 instances in 83 cases, while Levine found 38 in his series of 46 cases. Comparison of several series is given in table 12, where it is found that 45 per cent of 698 cases had antemortem clots in the ventricle. The exact localization of mural thrombi and related data from the present series are outlined in table 13. The location followed the general distribution of infarcts. The septum was involved in slightly more than half of the cases in this series and embolism was abnormally frequent when a thrombus was attached to

TABLE XII
Intraventricular Thrombus After Infarction

Author	Number of Cases	Cases with Ventricular Thrombi	Per Cent
This series	300	142	47
Appelbaum and Nicolson	150	81	54
Lisa and Ring	100	34	34
Parkinson and Bedford	83	14	17
Levine	46	38	83
Wolff and White	19	7	37
	698	316	45

the septum. Emboli to the lungs occurred in 75 per cent of cases of right ventricular thrombi, but emboli were detected in only 34 per cent of cases where the thrombus was in the left ventricle.

Formation of mural thrombi is facilitated by early cessation of active muscular contraction in the infarcted area of the ventricle. In addition, when the infarct reaches the endocardial surface fibrin and exudate soon form. Rarely a mural thrombus may occur in a heart with marked coronary sclerosis and no gross infarct, though no such case was found in this series.

The fate of thrombi in cases which survive for long periods cannot be known surely until *intra vitam* diagnosis of mural thrombus is possible. A certain proportion are dislodged and become emboli. Some are gradually organized, especially if a large part of the underlying muscular tissue survives. There were 12 instances of old cardiac scars (with no mural thrombi) associated with peripheral infarcts where there was no local arterial disease. It seems reasonable to suppose that these were embolic in origin with perhaps dislodgment of the whole thrombus. There were cases with mural thrombi adherent to three year old scars of ventricular infarcts. Some of these had been covered by endothelium and had liquid centers.

Mural thrombi may interfere with normal cardiac function by mechanical interference with blood flow. There were such cases where several

chambers had large thrombi, and one case where a massive antemortem thrombus almost filled the entire left ventricular cavity

Data indicating the length of time necessary for the formation of mural thrombi, after infarction, are found in table 13. There were three who died within 24 hours after infarction and who had early mural thrombi. Thrombi were uncommon until the fourth day, after which they became increasingly frequent among cases dying within the first month after infarc-

TABLE XIII
Intracardiac Mural Thrombi

Location	Number of Cases
Left ventricle alone	102
Both ventricles	15
Right auricle	8
Left auricle and left ventricle	7
Right ventricle alone	6
Right auricle and left ventricle	5
Left auricle alone	3
Both auricles and left ventricle	3
Both auricles and both ventricles	2
Left auricle and both ventricles	1
Right auricle and right ventricle	1
	(51%) 153

Left ventricle involved 135 times (7 multiple)

Right " " 25 "

" auricle " 19 "

Left " " 16 "

Septum " 72 "

Multiple infarcts 34

Old " 49

Recent " 70

Time of Death After Infarction in Those With and Without Mural Thrombi

	Day							Week			Month		Old
	1	2	3	4	5	6	7	2	3	4	2	3	
Cases with mural thrombi	3	2	2	5	2	4	8	27	15	12	11	5	57
Cases with no mural thrombi	19	10	7	4	7	3	5	25	2	4	9	5	43

tion. Table 13 should be compared with table 1, which gives the date of embolic accidents.

Ventricular Aneurysm Though the early pathologists (Morgagni) did not distinguish clearly between cardiac dilatation and aneurysm, Bérard^o noted the latter. The incidence of ventricular aneurysm in any series varies with the assiduity of the pathologist, the criteria employed and the proportion of very recent cases included. The last two factors doubtless account for the disparity of 5 per cent (Lisa and Ring) and 38 per cent (Appelbaum

and Nicolson) in reported studies. In this series cases with a definite localized margin and diameter of 3 cm. were included. It was found that 10 per cent of all cases with infarction developed aneurysmal dilatation, and 14 per cent of cases surviving a month or more did so. It could not be shown that sex, age, hypertension or other factors predisposed to aneurysm. Aneurysm appeared proportionally in cases of constrictive and of occlusive coronary lesions. Thickness of the wall was not necessarily a factor because in some cases aneurysm appeared when the wall was 5 mm. thick, and in

TABLE XIV
Ventricular Aneurysm

Author	Number of Cases	Number of Aneurysms	Per Cent
This series	300	31	10
Appelbaum and Nicolson	150	57	38
Lisa and Ring	100	5	5
Parkinson and Bedford	83	5	6
Levine	46	3	7
Wolff and White	19	3	16
	698	104	15

TABLE XV
Aneurysm of Ventricle
31 cases

<i>Artery Involved</i>		
Left anterior descending		28
Right main		1
?		2
<i>Location</i>		
Anterior apex of left ventricle		22
" " " " " and septum		4
Posterior " " " "		3
Anterior base " " "		1
" apex of right and left ventricle		1
<i>Survived</i>		
Year or more		19
6-8 months		2
2-3 months		4
4-6 weeks		2
28, 26, 22, 17 days (1 each)		4

some cases of scar 1 to 3 mm. thick no bulge had occurred. Old pericardial adhesions appeared in 16 cases, mural thrombi in 23. Location followed the pattern for the whole group. Though 16 had multiple infarcts, in only three did aneurysm arise from the second infarct. Half of the cases lived a year or more after the infarct which produced the aneurysm and five died of unrelated non-cardiac complications.

Formation of aneurysm has been demonstrated by roentgen-ray within six to seven days after infarct formation by Shookhoff and Douglas³⁷. The earliest case in this series had an aneurysm 17 days after infarction, and there were three additional cases within four weeks. Clinical diagnosis of this condition was not made in the present series. Signs as described in

these cases followed no characteristic pattern and were not different in essentials from cases without aneurysm. Some clinical signs have been described by Libman²¹ and Medlar and Middleton²⁷. Roentgen-ray studies, especially fluoroscopic or roentgen-kymographic, seem most likely to be of value in distinguishing these cases from (1) enlarged or dilated hearts and (2) pericardial effusions. This is not merely an academic point because one case in this series died due to laceration of the aneurysm by the needle at an attempted paracentesis for pericardial effusion. In extenuation it must be said that some clear fluid had been withdrawn, so a small pericardial effusion complicated the picture. If routine roentgen-ray studies were made in all cases of infarction, aneurysms would probably be detected in a larger percentage and at an earlier time than is commonly believed. Such a procedure is not justifiable, however, unless an acute problem in diagnosis arises.

Calcification of the Infarct Hirschboeck¹³ has recently considered the infrequent finding of calcification of the myocardium after coronary occlusion and has cited the literature. In the present series extensive calcification of scars occurred in three cases. Two of these had aneurysm and old mural thrombi. One without aneurysm had old pericardial adhesions, as did one case with aneurysm. The average heart weight was 535 grams. One case survived four years, another one year, and the third for an unknown period. No roentgen-ray studies were made and the diagnosis was not suspected during life.

Spontaneous Rupture of the Ventricle Fascination with the dramatic episode of rupture of the heart has outweighed accuracy in observation in the very numerous case reports appearing in the earlier literature. Recently several excellent reports have appeared, notable among which are those of Krumbhaar and Crowell¹⁵ supplemented by Davenport¹¹, Beresford and Earl⁷ and Benson, Hunter and Manlove⁵. Incidence in postmortem studies varies with the type of material analyzed. The data on pertinent facts regarding rupture are found in table 16. It occurred in about 6 per cent of cases of infarction.

Little information is available concerning the time interval between infarction and rupture in reported cases. In a number of reports it appears that the episodes of infarction and rupture have been confused. The widely accepted belief that rupture occurs most frequently from the fifth to fourteenth days is based on Levine's¹⁷ nine cases. When the cases in this series and in his are compared, considerable differences are seen and it is found that most occurred in the first eight days with no special preponderance. Practically all did occur within two weeks of infarction. The earliest appeared 14 hours after the first symptom of pain in a previously asymptomatic woman of 47. The latest was 16 days after infarction. Before conclusions are drawn as to the time of rupture, more data should be gathered.

In this series there were nine women and eight men with cardiac rupture. Some form of arrhythmia was present in seven. No unusual association was found with hypertension, angina, failure or other conditions. Mural

TABLE XVI
Spontaneous Rupture of Ventricle

Artery Involved		Site of Rupture	
Left anterior descending	13	Anterior apex of left ventricle	12
Left circumflex	2	Lateral apex of left ventricle	2
Right main	2	Posterior base of left ventricle	2
		Septum	1

Heart Weight

2-300	3-400	4-500	5-600	gm	6-700	7-800	840 with pericardium
1	6	4	3		1	1	1

Time of Rupture After Infarction

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	?
Number of cases this series	1	3	1	2	1		3	1				2	1			1	1
Number of cases Levine		1			1	1	1	2						2			
Total	1	4	1	2	2	1	4	3				2	1	2		1	1

Incidence of Rupture

	Cases of Infarction	Number of Ruptures	Per Cent
This series	300	17	6
Appelbaum and Nicolson	150	9	6
Lisa and Ring	100	0	0
Parkinson and Bedford	83	5	6
Levine	46	9	20
Wolff and White	19	0	0
	698	40	6

thrombi were found in eight. The heart weight varied from 260 to 750 grams, the average, 588 grams. Whenever the record included observations on the circumstances immediately preceding rupture some form of activity was found. This varied from animated conversation to falling out of bed.

Survival after rupture fell into four periods. Two cases died instantaneously. They were probably similar to the sudden syncopal deaths without rupture. The nine cases where death occurred in a few minutes had signs of cardiac tamponade, acute "inflow stasis," sudden venous engorgement, cyanosis, severe respiratory embarrassment and other evidence of cerebral anoxemia. Survival lasted one to three hours in five cases. They had smaller tears in the heart and their ultimate death was also due to tamponade, though the disaster was not so rapidly lethal. The one case surviving eight days deserves particular attention because of the rarity of cases with this long survival. Classical infarction occurred while the patient, a 69 year old Russian Hebrew, was resting at night prior to bedtime, with crushing pain radiating down the left arm. This lasted six hours. Progress thereafter was uneventful until the fourth day, when in the hospital

sudden collapse occurred. There was gradual but only partial recovery and for eight days the patient suffered with increasing signs of congestive failure and finally died. At autopsy the heart was closely adherent to the pericardium, attached by means of a thick clot of organizing blood. A smooth rupture 3.5 by 3 cm. along the lateral margin of the left ventricle was in communication with a narrow sinus in the organizing tissue. The specimen weighed 840 grams. The tear was considered to be about a week old, with evidence of healing and endothelialization.

Embolism of a Coronary Artery A critical review of coronary embolism has recently been made by Saphir³⁴. The rarity of authentic cases is noted. In four cases in the present series coronary embolism from friable valvular vegetations seemed certain and in an additional case it is probable that an older embolism had caused infarction. Data on these cases are found in table 17. Contrary to Saphir's finding, sudden death did not occur,

TABLE XVII
Coronary Embolism

Number	Age	Sex	Pain	Failure	Heart	L K G	Survival	Valves Involved	Artery	Heart Weight grams	Other Embolic Manifestations
1	78	F	Epigastric left arm	Slight	E	S A Tachycardia 136	16 days rupture	Soft friable vegetation on aortic leaf of mitral	Left circumflex	260	0
2	69	M	Left shoulder Left arm	Moderate	E		12 days	Fungating vegetation on mitral	Left anterior descending (with some sclerosis)	520	Spleen Kidney
3	50	M	Substernal Left arm	0		Coronary disease	3 hours	Aortic stenosis with vegetation	Left anterior descending	480	?
4	35	F	Chest	0	E		12 hours	Aortic cusps crumbly vegetation	Right main	310	Spleen
(?)	65	F	Substernal	Slight			old?	Mitral valve Friable vegetation	Left anterior descending (some sclerosis)	335	Brain Kidney Mesentery

though one case died in three hours and one in 12 hours after the accident. These cases were not studied carefully clinically because those surviving the first day were moribund on admission. If the diagnosis in the questionable case be correct, it indicates that coronary embolism is not necessarily fatal. In this connection it should be noted that four of the five cases were over 50. The two youngest cases died soon after embolism occurred. Every case had some coronary sclerosis and presumably had developed collateral circulation. This is in agreement with Gross' belief in the increased efficiency of collateral circulation in older individuals.

Auricular Infarcts It is improbable that the rarity of reported cases of infarction of the auricle is a true indication of its incidence. There were

two definite cases in this series and one additional case of a small scar in the auricular appendage in a case of syphilitic infarct of left ventricle Clowe and his associates⁹ reported a case of rupture of the right auricle and analyzed the literature on auricular rupture, which revealed that the right auricle was perforated over twice as frequently as the left, in sharp contradistinction to the localization in ventricular rupture In this series one clear cut case showed perforation occurring in the left auricle with especially prominent subepicardial necrosis, along with an embolic infarct of the left ventricle with final rupture No auricular thrombi were found In the other case the right coronary was the site of a completely occluding thrombosis and there was an infarct in the posterior basilar aspect of the right and left ventricles In addition, there was a large area adjacent to this where the right auricle had undergone hemorrhagic infarction Pericarditis was found over both auricle and ventricle, and this case had auricular fibrillation

Pericarditis and Pericardial Effusion While localized pericarditis in heart disease was observed by Morgagni and, associated with more specific lesions, by Berard, its nature was not comprehended until the pathology of infarction was studied Ziegler and von Leyden gave good descriptions Sternberg's comprehensive review of "pericarditis epistenocardia" covers the field down to his time Data available from this series are tabulated and compared with several groups from the literature, as seen in table 18 (See also table 15—part II) The lesion was observed in 28 per cent of all cases collected, and in 32 per cent of this series

Pericardial effusion as a complication of infarct is rare^{36, 25} and it is probable that the most important factor in its production is congestive failure There were 44 cases in this series with an effusion larger than 50 c c (table 18) In 17 of these there was no fresh pericarditis, but in every case there was some degree of failure

Hydrothorax Pleural transudation appeared in many cases as a sequel to congestive failure In 47 cases it was equal on both sides and in 48 greater on the right (average difference 750 c c) There were eight cases with larger effusions on the left (average difference 275 c c) No morphological constant was found in the hearts Most, but not all, had preponderant left ventricular damage, and râles had been heard in practically all cases examined during formation of hydrothorax

SUMMARY

- 1 Congestive failure and shock followed in more than half of the acute attacks Enlarged liver and jaundice were observed in a small proportion of cases

- 2 Peripheral embolism was found most frequently in the second, third and fourth weeks Many incidents considered clinically to be embolic were found to depend on local vascular faults

- 3 No specific prognostic gauge was found to be valid in an individual case

TABLE XVIII
Lesions of Pericardium

Fresh fibrinous pericarditis	52
Old adhesions	32
Obliterating adhesions (not constricting)	6
Old and fresh pericarditis	3
Fresh obliterating pericarditis	3
Purulent pericarditis	2
"Uremic" pericarditis	2
"Organizing" clot after rupture	1

Effusion

cu cm	
50-75	10
75-100	16
100-150	5
150-200	6
200-250	4
250-300	2
400	1

Autopsy Findings of Pericarditis

Author	Number of Cases	Pericarditis
Huchard	31	7
Wearn	19	4
Wolff and White	23	11
Parkinson and Bedford	83	11
Levine	46	24
Lisa and Ring	100	10
Appelbaum and Nicolson	150	50
This series		
Recent	189	58
Old	111	41*
	752	213*

* 3 cases had old and recent

TABLE XIX
Hydrothorax

	per cent	Average cc	Range cc
Present in 163 of 300	54		
* Bilaterally equal	47	575	100-2000
* Right side alone	15	700	100-2200
* Right greater than left	33		
Right side		1250	200-2800
Left side		500	100-1600
* Left greater than right	8		
Right		275	0-1000
Left		550	100-1500

* Cases which may have been influenced by pulmonary infarct, pleural infection, or obliterative pleural adhesions were discarded

4 Causes of death were investigated and the predisposing influence of syncopal attacks was noted in cases of sudden death. Seasonal variation of death was in part influenced by seasonal fluctuation in incidence of acute attacks.

5 The left coronary tree was seriously involved in 84 per cent of cases, the right in 21 per cent. Nine cases of "ectopic infarction" appeared.

6 Twenty per cent of the infarcts followed arterial narrowing without thrombosis.

7 In four cases no arterial damage was detected.

8 Eight cases of coronary anomalies were found, one with a small coronary aneurysm.

9 The heart was enlarged in 83 per cent of the cases. The largest hearts were found in hypertensives.

10 Ventricular mural thrombi were found in nearly half the cases, emboli were detected twice as frequently in instances of right ventricular thrombi as in cases of mural thrombosis of the left ventricle. Some thrombi were present three years after acute infarction. Embolism was most frequent when the thrombus was attached to the interventricular septum.

11 Ventricular aneurysm was found in 10 per cent of the cases and appeared as early as the seventeenth day after infarction.

12 There were three cases of extensive calcification of scars.

13 Spontaneous rupture of the ventricle occurred in 17 cases. One survived rupture eight days. In one case an aneurysm was ruptured by a needle.

14 Four cases of coronary embolism from friable valvular vegetations were found, and there was one probable case in addition.

15 There were two auricular infarcts.

16 Pericarditis was found in 32 per cent of the cases and an effusion of 50 c c or more, in 15 per cent.

17 Hydrothorax was frequent, and in many cases was greater on the right.

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BIBLIOGRAPHY

- 1 ALIBUTT, C. Diseases of the arteries, including angina pectoris, 1915, London.
- 2 APPELBAUM, E., and NICOLSON, G. H. B. Occlusive diseases of the coronary arteries, *Am Heart Jr*, 1935, *v*, 662.
- 3 BARNES, A. R., and BALL, R. G. The incidence and situation of myocardial infarction in one thousand consecutive postmortem examinations, *Am Jr Med Sci*, 1932, *CLXXXIII*, 215.
- 4 BARTELS, E. C., and SMITH, H. L. Gross cardiac hypertrophy in myocardial infarction, *Am Jr Med Sci*, 1932, *CLXXXIV*, 452.
- 5 BENSON, R. L., HUNTER, W. C., and MANLOVE, C. H. Spontaneous rupture of the heart, *Am Jr Path*, 1933, *IX*, 295.

- 6 BERARD, P H Paris Thesis, No 23, 1826
- 7 BERESFORD, E H, and EARL, C J C Spontaneous cardiac rupture a review of 46 cases, Quart Jr Med, 1930, *xliv*, 55
- 8 BLUMER, G Pericarditis epistenocardia, Jr Am Med Assoc, 1936, *cvi*, 178
- 9 CLOWE, G M, KELLERT, E, and GORHAM, L W Rupture of the right auricle of the heart, Am Heart Jr, 1934, *ix*, 324
- 10 CORVISART, J N Essai sur les maladies et les lesions organiques du coeur, Paris, 1806 (Gates Translation, 1812)
- 11 DAVENPORT, A B Spontaneous heart rupture a statistical summary, Am Jr Med Sci, 1928, *clxvi*, 62
- 12 HARRISON, T F Failure of the circulation, 1935, Williams and Wilkins Company, Baltimore
- 13 HIRSCHBOECK, F J Calcification of the myocardium following coronary occlusion, Am Heart Jr, 1934, *x*, 265
- 14 HUCHARD, H Traite clinique des maladies du coeur et de l'aorte, 1899, Paris, Ed 3
- 15 KRUMBHAR, E B, and CROWELL, C Spontaneous rupture of the heart, Am Jr Med Sci, 1925, *clxx*, 828
- 16 LEARY, T Coronary spasm as a possible factor in producing sudden death, Am Heart Jr, 1935, *x*, 338
- 17 LEVINE, S A, and BROWN, C L Coronary thrombosis its various clinical features, Medicine, 1929, *viii*, 245
- 18 LEVY, R L, and BRUENN, H G Acute fatal coronary insufficiency, Jr Am Med Assoc, 1936, *cvi*, 1080
- 19 LEWIS, T Diseases of the heart, 1933, Macmillan Company, New York
- 20 VON LEYDEN, E Über die Sclerose der Coronar-Arterien und die davon abhängigen Krankheitszustände, Ztschr f klin Med, 1884, *vii*, 459
- 21 LIBMAN, E Methods of physical examination with special reference to painful disease of the thorax and abdomen, Interstate Postgraduate Med Assoc N Am, Cleveland Proc, Oct 1926, 60
- 22 LISA, J R, and RING, A Myocardial infarction or gross fibrosis (analysis of one hundred autopsies), Arch Int Med, 1932, *i*, 131
- 23 LONGCOPE, W T The effect of occlusion of the coronary arteries on the heart's action and its relationship to angina pectoris, Ill Med Jr, 1922, *xl*, 186
- 24 MACCALLUM, W G, and TAYLOR, J S The typical position of myocardial scars following coronary obstruction, Bull Johns Hopkins Hosp, 1931, *xl*, 256
- 25 MASTER, A M, and JAFFE, H L Coronary artery thrombosis with pericardial effusion, Jr Am Med Assoc, 1935, *civ*, 1212
- 26 MASTER, A M, DACK, S, and JAFFE, H L Coronary thrombosis an investigation of heart failure and other factors in its course and prognosis, Am Heart Jr, 1937, *xiii*, 330
- 27 MEDLAR, E M, and MIDDLETON, W S Aneurysm of the left ventricle, Am Heart Jr, 1927-8, *iii*, 346
- 28 MORGAGNI, J G De Sedibus et Causis Morborum, Venetus, II Epist 24 et seq 1761 (Translated by Benjamin Alexander, London, 1769)
- 29 PALMER, J H The prognosis following recovery from coronary thrombosis with special reference to the influence of hypertension and cardiac enlargement, Quart Jr Med, 1937, *xxx*, 49
- 30 PALMER, J H The size of the heart after coronary thrombosis, Canad Med Assoc Jr, 1937, *xlvi*, 387
- 31 PARDEE, H E B, et al Discussion at American Heart Association Meeting, June 1934, Am Heart Jr, 1935, *x*, 406
- 32 PARKINSON, J, and BEDFORD, D E Cardiac infarction and coronary thrombosis, Lancet, 1928, *i*, 4

- 33 SALZMANN, H A Spontaneous rupture of the heart simulating surgical abdominal disease, *Am Jr Med Sci*, 1934, clxxxviii, 347
- 34 SAPHIR, O Coronary embolism, *Am Heart Jr*, 1933, viii, 312
- 35 SAPHIR, O, PRIEST, W S, HAMBURGER, W W, and KATZ, L N Coronary arteriosclerosis, coronary thrombosis, and the resulting myocardial changes, *Am Heart Jr*, 1935, x, 567, 1935, x, 762
- 36 SCHWARZ, S P Pericardial effusion following acute coronary vessel closure, *Am Heart Jr*, 1934, x, 253
- 37 SHOOKHOFF, C, and DOUGLAS, A H A case of acute coronary occlusion with roentgenographic evidence of the early development of an aneurysm of the left ventricle, *Am Heart Jr*, 1931, vii, 95
- 38 STERNBERG, M Pericarditis epistenocardia, *Wien med Wehnschr*, 1910, lx, 14
- 39 WARNER, W P, and DAUPHINLE, J A Thrombosis of a coronary venous sinus in a case of thrombophlebitis migrans, *Am Heart Jr*, 1936, xii, 483
- 40 WEARN, J T Thrombosis of the coronary arteries with infarction of the heart, *Am Jr Med Sci*, 1923, clxv, 250
- 41 WEIGERT, C *Virchow's Arch f path Anat*, 1880, lxxx, 106
- 42 WEISS, S, and BAKER, J P Carotid sinus reflex in health and disease, *Medicine*, 1933, xii, 297
- 43 WEISS, S Syncope and related syndromes, *Oxford Med*, 1935, ii, 250
- 44 WHITTEN, M B The relation of the distribution and structure of the coronary arteries to myocardial infarction, *Arch Int Med*, 1930, xliv, 383
- 45 WOLFF, L, and WHITE, P D Acute coronary occlusion report of twenty-three autopsied cases, *Boston Med and Surg Jr*, 1926, cxv, 13
- 46 ZIEGLER, ERNST Ueber Myomalacia Cordis, *Virchow's Arch f path Anat*, 1882, xc, 211

THE PRESENT STATUS OF METHODS FOR THE PROPHYLAXIS OF ACUTE ANTERIOR POLIOMYELITIS

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ACUTE anterior poliomyelitis is still among the important diseases in which knowledge of the mechanism of infection, its mode of dissemination and the factors responsible for epidemics, as well as the nature of natural and acquired immunity, is quite incomplete and controversial in many particulars and especially in relation to methods of prophylaxis

Twenty-eight years ago Flexner and Lewis¹ first suggested that infection occurred through the upper respiratory tract and especially by way of the olfactory nerves. At least monkeys can be successfully inoculated by intranasal instillations of the virus and in spite of technical difficulties this virus has been found in the nasal and oropharyngeal washings of a small but sufficient number of human beings during and after attacks of the disease as well as in healthy individuals^{2, 3, 4, 5} to indicate that the upper respiratory tract is at least one avenue of infection, although the fact that epidemics commonly occur during July, August and September is not in conformity with what is observed in many other diseases transmitted by droplet or upper respiratory tract secretions for the highest incidence of such infections is more encountered during the colder months of the year. Furthermore, virus injected intracerebrally and intravenously in monkeys has been found in the oropharyngeal mucosa and washings suggesting that in human beings it may be excreted or eliminated as well as absorbed in these areas. More recent investigations by Schultz and Gebhardt,⁶ Lennette and Hudson,⁷ Gordon and Lennette,⁸ Sabin and Olitsky⁹ and others have definitely confirmed earlier observations that in monkeys the virus is absorbed by way of the olfactory tracts. The big and important question, however, and especially in relation to prophylaxis in human beings by nasal instillations of chemical agents for the blockage or destruction of virus, is whether the olfactory area is the *only* avenue of infection or whether this may include the upper respiratory tract in general. The latter possibility is suggested by the fact that the disease has been produced experimentally in monkeys by intratracheal inoculation with virus, as well as by the fact that the virus has been found in the tonsils and nasopharyngeal mucosa^{4, 10} of both human beings and monkeys.

Much stress has been laid upon the olfactory area as the portal of entry of the virus on the basis that section of the olfactory tracts prevents infection of monkeys inoculated intranasally and because Landon and Smith¹¹

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have found pathological changes in the tracts and bulbs of some human beings succumbing to the disease. Microscopical examination of 56 olfactory bulbs by these investigators, however, "has shown a surprisingly small amount of pathological change. There has frequently been edema and congestion, harbingers of more extensive damage, but in less than a fourth of them, do the characteristic cellular and infiltrative changes, as seen in the ganglia and nerve roots, appear. Either any inflammatory reaction in these organs is extremely short-lived, unlike the lesions of poliomyelitis elsewhere in the central nervous system, or the virus passes along these structures without leaving its identifying signature. A third possibility, which strikes us as more logical, in view of the essential difference in the nature of the pathological lesions, is that the olfactory bulb in human beings is not necessarily as frequent a pathway for the virus as is commonly held, and that nerve roots elsewhere are equally important portals of entry, possibly indirectly by way of the blood stream to their ganglia." Thus do these investigators with commendable conservatism conclude from their studies that the pathways of distribution of the virus do not seem to be as simply explained in human beings as in monkeys since they are inclined to the belief "that only direct extension by way of the nasopharynx and other nerve roots, but also the gastrointestinal tract and blood stream must be considered as very significant factors." In this connection it may be stated that Harmon and his colleagues¹² have failed to find histological changes of infection in the olfactory bulbs of nine cases of the 1936 Chicago epidemic. Under the circumstances I believe that in the present state of our knowledge we must suspect the possibility that infection with the virus takes place from the nasopharyngeal mucosa and even from the trachea in general as well as through the olfactory area and must agree that definite and recognizable tissue changes may not be produced by the virus in the avenues of infection.

If this is true the application of chemical agents to the olfactory area alone for the destruction of virus or the blockage of its absorption could not be expected to prove completely effectual as a prophylactic measure in human beings.

Unquestionably Sabin, Olitsky and Cox,¹³ Armstrong and Harrison,¹⁴ Schultz and Gebhardt^{15, 16} and others have effectually prevented infection of monkeys inoculated intranasally with virus by treatment of the olfactory area with picric acid and alum and particularly with zinc sulphate, but the picric acid-alum spray failed as a practical prophylactic measure in the Alabama epidemic of 1936 and the same may be stated in the case of the zinc sulphate mixture in the Toronto epidemic of 1937.¹⁷ It is true, however, that nasal spraying with picric acid and alum soon got out of control in Alabama so that a fair trial was impossible although even under these circumstances Armstrong¹⁸ thought that the actual incidence of poliomyelitis in the sprayed groups (25 cases) was somewhat less than the calculated incidence based on the attack rate in the unsprayed control group of the Birmingham area. Furthermore, in the Toronto epidemic, Tisdall and his

colleagues,^{19, 20} while employing the method of Peet, Echols and Richter,²¹ found it impractical to give treatment on three successive days but succeeded in giving two applications approximately 12 days apart. Of 4713 children treated in this manner with 0.5 to 1 c.c. of the mixture of 1 per cent zinc sulfate, 1 per cent pontocaine and 0.5 per cent sodium chloride solution, 11 developed poliomyelitis while 18 cases developed in an untreated control group of 6300. This difference in the attack rate is not statistically significant and while anosmia occurred in but 25 per cent as evidence of complete and effectual treatment of the olfactory area, yet the Toronto group of 44 otolaryngologists conducted the field investigation with such thoroughness and skill that in my opinion the results are a good and acceptable indication of what is to be expected from the solution and method of treatment employed. It is to be regretted, however, that three daily applications could not be employed as has been found effectual in monkeys but headache and other temporary disturbances made this impossible as a practical procedure. Whether or not treatment of the total olfactory area of human beings as indicated by complete anosmia will prove more effectual as a prophylactic measure remains to be determined and I think final judgment of the value of prophylaxis by applications of zinc sulfate to the olfactory area should await its trial under such conditions. But I doubt if an additional field trial of treatment with the DeVilbiss atomizer inserted between the nasal septum and middle turbinate will give any better results than observed by the Toronto group. For this reason a trial of the method proposed by Pentecost,²² consisting of the injection of 0.5 c.c. of the solution by means of a flexible olive tipped catheter with the head well down in the Proetz position, appears advisable since he reports that complete anosmia is obtained persisting for five days or longer without danger of possible injury to the mucosa or cribriform plate and with little likelihood of the solution entering the sphenoidal sinus or being swallowed. Nevertheless headache was noted in every case persisting for 2 to 6 hours and especially severe in individuals over 12 years of age, and there was stuffiness of the nose for 6 to 12 hours.

It is practically certain therefore that spraying of the nose with atomizers by the laity has failed and that the method of Peet and his colleagues cannot be successfully used on a broad scale since complete treatment of the olfactory area is difficult to obtain. Furthermore, it is not without hazard in unskilled hands. The catheter method employing the solution of zinc sulfate may prove more effectual although frontal headache may be severe and the anosmia may persist for months, especially in adults, suggesting either destruction of the olfactory endings, persistent edema or some other change as yet undetermined.²³ Nevertheless one or more applications of 1 per cent zinc sulfate solution may be worthy of trial during the next epidemic but the method is certainly of no value in the prophylaxis of sporadic cases and offers little or no hope of ultimately eliminating the disease.

Furthermore, I am personally prepared for disappointing results if it is true that virus may be absorbed from areas of the upper respiratory tract other than the olfactory area. Whether or not infection may occur through the skin and gastrointestinal tract is even more uncertain but both the possibility and probability are to be admitted. So far we have not been able to infect *Macacus rhesus* monkeys by feeding large doses of the M V strain of virus or by instilling by stomach tube as much as 10 to 20 c c of a 10 per cent suspension of monkey poliomyelitic spinal cord. It may be that *Macacus cynomolgus* is more susceptible to infection by this route²⁴ but the literature is quite controversial and indefinite²⁵. Certainly it appears that the virus may escape destruction in the stomach and intestines of both monkeys and human beings since it has been found in the feces by several investigators²⁶ and more recently by Harmon¹² and Kramer,²⁷ but whether it represents merely swallowed virus or whether its presence indicates a gastrointestinal avenue of infection cannot be definitely stated at the present time. Toomey,^{28, 29} who has properly called attention to the late summer and autumnal prevalence of the disease as suggestive of its gastrointestinal origin and who has succeeded in producing it experimentally in monkeys by special methods of inoculation, believes that the toxins of enteric organisms and certain vitamin deficiencies may facilitate infection by this route but Hudson, Lennette and Gordon^{30, 31} have failed to infect monkeys by placing large amounts of virus in isolated loops of intestine. Under the circumstances it is commonly thought that the normal gastrointestinal tract of the monkey offers a barrier to infection^{32, 33} but that extraordinary measures, such as clamping the gut until the pinch reflex disappears and injecting the virus subserosally, may result in infection since under these circumstances virus may be absorbed by unmyelinated nerve fibers as it may in other parts of the body.

In other words, the general results of experimental investigations with monkeys strongly suggest that the virus is transported to the central nervous system by way of the axons of nerves from the portal of infection. It is certainly to be admitted moreover that most strains of the virus possess a striking selective affinity for these tissues and especially for those anterior horn cells of the spinal cord in which tetanus toxin also, regardless of the site of initial infection, tends to localize selectively. However, the possibility that the virus is absorbed through the mucosa of the upper respiratory tract into the lymphatics and blood with secondary localization in the central nervous system in a manner analogous to the pathogenesis of meningococcus meningitis is not to be lightly dismissed. It is true that the virus has not been detected so far in the blood of human cases of poliomyelitis but several investigators have found it in the blood of infected monkeys³⁴ and it is to be admitted that such technical difficulties are involved that small amounts of virus in the blood of human beings may escape detection. Burrows³⁵ has marshalled considerable data indicating that poliomyelitis may be essentially

and primarily an infection of the reticulo-endothelium of the body and Landon and Smith³⁶ on the basis of their thorough pathological studies in the 1931 epidemic in New York City state that, "whether the virus gains access to the central nervous system entirely by direct extension along the nerves of the nasopharynx, or entirely by way of the blood stream or both, we are inclined to believe that the systemic involvement of the reticulo-endothelial tissues plays an important part in the distribution of the lesions." Furthermore, if it is true that microglia and histiocytes are morphologically and functionally identical as stated by Dunning and Furth³⁷ it may be that the selective affinity of poliomyelitis virus for the tissues of the central nervous system is only an expression of its affinity for the reticulo-endothelium of the body in general and support the hypothesis that the disease is primarily an infection of this system.

In other words it appears on the basis of animal experiments that the upper respiratory tract is at least one important avenue of infection with absorption of virus by way of the olfactory nerves to the central nervous system but I do not think there is sufficient evidence for the assumption that the olfactory area is the sole pathway of infection. It appears both possible and probable that the virus may be absorbed from other areas of the respiratory tract and from any other portal initially infected and be transmitted by way of the axons of nerves or by way of the lymphatics and blood with consequent infection of the reticulo-endothelial tissues and central nervous system. For these reasons I have long thought that the greatest hope of successful prophylaxis of the disease lay in vaccination or active immunization.

That monkeys can be successfully vaccinated against acute anterior poliomyelitis has been amply proved by many investigators and especially with vaccines prepared of monkey poliomyelitic spinal cords carrying living or active virus. Unfortunately vaccines containing heat or chemically killed virus have not proved as effective as those incorporating at least some living virus. Brodie and Park³⁸ have found in both monkeys and children that virus treated with formalin for the minimum amount of time for rendering it non infective possessed some immunizing value. In my laboratory vaccines prepared of 4 per cent suspensions of monkey spinal cord carrying the M V strain of virus treated with 1 per cent sodium ricinoleate and administered by subcutaneous and intracutaneous injection have successfully immunized monkeys against both intracerebral and intranasal inoculation with virus^{40, 41, 42}. Of a total of 183 animals, 3 or 1.1 per cent developed paralysis during the period of immunization. All of these three occurred among the 124 animals given subcutaneous injections of the vaccine while none of 59 animals given intracutaneous injections developed any evidences of infection during immunization. It was my hope that this strain of virus had lost infectivity for human beings by reason of its long adaptation to the monkey, and especially after treatment with sodium

ricinoleate and when given by subcutaneous injection,⁴³ but the occurrence of nine cases of poliomyelitis among 10,725 individuals given the vaccine in 1935⁴⁴ has indicated that the virus apparently possesses infectivity for human beings and that this vaccine as well as the formalized vaccine of Park and Brodie is too dangerous for use⁴⁵

I am convinced, however, that there is little or no hope of safe and effective vaccination against the disease unless active virus is employed. But the fact that considerable evidence has now accumulated to show that immunologically specific strains of virus may exist^{46, 47, 48, 49, 50} and that some of these may be highly infective by subcutaneous injection complicates the problem although it may be ultimately solved by vaccines made from cultures of living virus of non-neurotropic strains. The fact that one attack of the disease appears to leave a lasting immunity in the great majority of instances,^{51, 52} although second attacks may not be as rare as hitherto surmised,⁵³ and that the low attack rate among adults may be due to acquired immunity from a wide distribution of the virus with latent or clinically undetectable attacks of the disease with the development of antiviral antibody in the blood and placental extracts, still leaves one with considerable hope that vaccination may ultimately solve the problem of prophylaxis.

That vaccines and especially those containing living virus are capable of engendering the production of antiviral antibody is generally admitted but the ability of the antibody to prevent infection of the central nervous system has been questioned^{54, 55}. Over 90 per cent of monkeys immunized with vaccines of living virus by various investigators have shown the presence of this antibody in the blood on the basis of serum neutralization tests⁵⁶ and in my laboratory the majority immunized with ricinoleated vaccine were found completely protected against the intracerebral injection of virulent virus. Therefore, while I believe that the natural and acquired immunity of the disease is largely of the cellular or tissue type, yet it appears to be due in part at least to humoral resistance which may be ascribed to the presence of antiviral antibody in the blood.

Whether or not the antiviral antibody to be found in the blood of normal persons and of convalescents and in placental extracts possesses prophylactic value in human beings cannot be definitely stated. So far there has not been a sufficiently extensive and properly controlled study of it in this connection. Indeed this seems to be impossible insofar as convalescent serum is concerned. Under the circumstances I think we can and should base an opinion on the results of the use of such sera and extracts in the prophylaxis of the disease in monkeys inoculated both intracerebrally and intranasally with infective amounts of virus. On the basis of such evidence I believe that normal and convalescent sera containing large amounts of antibody have undoubtedly demonstrated their prophylactic activity when given in sufficiently large doses⁵⁶. When the virus has actually attacked the cells of the central nervous system it appears to be beyond neutralization by antibody.

as is under like circumstances the toxin of *Clostridium tetani* by tetanus antitoxin. I believe, however, that the virus of poliomyelitis may be effectually neutralized by antiviral antibody before such cellular invasion has occurred, although failures^{57, 58} are to be expected in this as in passive immunization against other acute infections with their respective immune sera. It is true that the therapeutic value of normal and convalescent serum has not been reflected in statistical studies but I am among the large number of physicians who believe that they have seen many individual cases where the early administration of serum and particularly blood transfusion may have effectually prevented progressive infection of the spinal cord. Not without interest in this connection is a recent report of Jackson¹⁷ on the use of serum in the 1936 epidemic in Manitoba stating that the injection of 20 c c in 395 cases within 36 hours to 4 days before the onset of paralysis resulted in the recovery of 86.1 per cent without residual paralysis and a mortality rate of 4.6 per cent as contrasted with 36.1 per cent residual paralysis and a mortality of 11.8 per cent among a group of 119 cases to whom serum was not given at all or after the onset of paralysis.

I believe therefore that the intramuscular injection of 20 to 40 c c of normal or convalescent serum known to contain antibody on the basis of monkey serum neutralization tests is still a hopeful prophylactic measure in children. The duration of the passive immunity is unknown but by analogy with other diseases probably does not last for over four weeks so that during epidemics two or more injections are required for sufficiently prolonging the degree of protection.

In conclusion brief reference may be made to the urgent need of a practical and clinically applicable test for susceptibility to poliomyelitis in view of its low attack rate. If such were available it would facilitate and greatly encourage efforts toward its prophylaxis not only with vaccines and sera but by the local treatment of the olfactory area with chemical agents as well. The problem is one of such importance as to richly merit the attention and efforts of investigators of this disease. Unfortunately the monkey serum neutralization test is at best only a rough measure of humoral immunity with no bearing at all upon the far more important phase of cellular or tissue resistance. It is, moreover, too expensive and time consuming for any possible practical application⁵⁹. Various skin tests^{60, 61, 62} as well as complement fixation, precipitin and other reactions⁶³ have proved without value. We believe, nevertheless, that the problem may not be beyond ultimate solution.

SUMMARY

1. The results of experimental studies in poliomyelitis of monkeys show that the virus is absorbed by way of the olfactory nerves and microscopical examination of the olfactory bulbs in human cases of the disease also suggests that this is at least one avenue of infection in human beings.

2 Chemo-prophylaxis in human beings by the application of mixtures of picric acid and alum or of zinc sulfate to the olfactory area has failed but this may have been due to incomplete application of these agents

3 Under present conditions the further trial of solutions of zinc sulfate is recommended by a method insuring more adequate treatment of the olfactory area

4 It is possible, however, that the virus of poliomyelitis may be absorbed from the oropharyngeal mucosa, tonsils, trachea and even the intestinal tract and if this occurs in human beings treatment of the olfactory area alone cannot be expected to prove effective in the prophylaxis of the disease

5 Monkeys have been successfully immunized against poliomyelitis with vaccines of the virus and especially those containing active virus but these are considered too dangerous for the vaccination of human beings

6 Antiviral antibody contained in normal and convalescent human sera and placental extracts is capable of protecting monkeys against experimental poliomyelitis when administered in sufficiently large amounts. On this basis it appears quite probable that the antibody possesses some prophylactic value in human beings if administered before the virus has attacked the central nervous system

7 In view of the low attack rate of poliomyelitis a practical test for susceptibility is urgently required since such would greatly facilitate the selective use of chemo-prophylaxis as well as prophylaxis by active and passive immunization. At the present time, however, such a test has not been discovered. The monkey serum neutralization test is not acceptable in this connection not only because of its expense and the time required to carry it out but likewise because it is not a measure of the more important cellular or tissue resistance of the disease

BIBLIOGRAPHY

- 1 FLENER, S, and LEWIS, P A Epidemic poliomyelitis in monkeys, Jr Am Med Assoc, 1910, liv, 45
- 2 PAUL, J R, and TRASK, J D The detection of poliomyelitis virus in so-called abortive types of the disease, Jr Exper Med, 1932, lvi, 319
- 3 PAUL, J R, TRASK, J D, and WEBSTER, L T Isolation of poliomyelitis virus from the nasopharynx, Jr Exper Med, 1935, lxi, 245
- 4 KRAMER, S D Detection of a healthy carrier of virus of poliomyelitis without history of contact, Proc Soc Exper Biol and Med, 1935, xxxii, 1165
- 5 KRAMER, S D, SOBEL, A E, GROSSMAN, L H, and HOSKWITH, B Survival of the virus of poliomyelitis in the oral and nasal secretion of convalescents, Jr Exper Med, 1936, lxiv, 173
- 6 SCHULTZ, E W, and GEBHARDT, L P Olfactory tract and poliomyelitis, Proc Soc Exper Biol and Med, 1934, xxxi, 728
- 7 LENNETTE, E H, and HUDSON, N P Relation of olfactory tracts to intravenous route of infection in experimental poliomyelitis, Proc Soc Exper Biol and Med, 1935, xxxii, 1444
- 8 GORDON, F B, and LENNETTE, E H The blood stream in experimental poliomyelitis, Jr Bacteriol, 1938, xxxv, 43

- 9 SABIN, A B, and OLITSKY, P K Fate of nasally instilled poliomyelitis virus in normal and convalescent monkeys, Jr Bacteriol, 1938, *xxv*, 44
- 10 FAIRBROTHER, R W, and HURST, E W The pathogenesis of, and propagation of the virus in, experimental poliomyelitis, Jr Path and Bact, 1930, *xxiii*, 17
- 11 LONDON, J F, and SMITH, L W Poliomyelitis Based on a study of the 1931 epidemic in New York City, 1934, MacMillan Company, New York, p 50
- 12 HARMON, P H The use of chemicals as nasal sprays in the prophylaxis of poliomyelitis in man, Jr Am Med Assoc, 1937, *cix*, 1061
- 13 SABIN, A B, OLITSKY, P K, and COX, H R Protective action of certain chemicals against infection of monkeys with nasally instilled poliomyelitis virus, Jr Exper Med, 1936, *lxiii*, 877
- 14 ARMSTRONG, C, and HARRISON, W T Prevention of experimental intranasal infection with certain neurotropic viruses by means of chemicals instilled into the nostrils, Pub Health Rep, 1936, *li*, 203
- 15 SCHULTZ, E W, and GEBHARDT, L P Prevention of intranasally inoculated poliomyelitis in monkeys by previous intranasal irrigation with chemical agents, Proc Soc Exper Biol and Med, 1936, *xxxiv*, 133
- 16 SCHULTZ, E W, and GEBHARDT, L P Zinc sulfate prophylaxis in poliomyelitis, Jr Am Med Assoc, 1937, *cviii*, 2182
- 17 JACKSON, F W The 1936 epidemic of poliomyelitis in Manitoba control measures, Canada Health Jr, 1937, *xxviii*, 363
- 18 ARMSTRONG, C Experience with picric acid-alum spray in the prevention of poliomyelitis in Alabama, 1936, Am Jr Pub Health, 1937, *xxvii*, 103
- 19 TISDALL, F F, BROWN, A, DEFRIES, R D, ROSS, M A, and SELLERS, A H Zinc-sulphate nasal spray in the prophylaxis of poliomyelitis, Canada Pub Health Jr, 1937, *xxviii*, 523
- 20 TISDALL, F F Nasal spraying as a preventive of poliomyelitis, Canada Pub Health Jr, 1937, *xxviii*, 431
- 21 PEET, M M, ECHOLS, D H, and RICHTER, H J The chemical prophylaxis for poliomyelitis The technic of applying zinc sulfate intranasally, Jr Am Med Assoc, 1937, *cviii*, 2184
- 22 PENTECOST, R S Zinc sulphate as a chemo-prophylactic agent in epidemic poliomyelitis, Canada Pub Health Jr, 1937, *xxviii*, 493
- 23 SABIN, A B, and OLITSKY, P K Mode of action of zinc sulfate spray in preventing infection with nasally instilled poliomyelitis virus, Jr Bacteriol, 1938, *xxv*, 44
- 24 LEVADITI, C, KLING, C, and LEPINE, P Nouvelle recherches experimentals sur la transmission de la poliomyelite par la voie digestive Action du chlore sur le virus poliomyelitique, Bull Acad de med, 1931, *cv*, 190
- 25 International Committee for the Study of Infantile Paralysis, 1931, Williams and Wilkins Company, Baltimore, p 85 and 257
- 26 See reference 25, page 78
- 27 KRAMER, S D Personal Communication
- 28 TOOMEY, J A Active and passive immunity and portal of entry in poliomyelitis, Jr Am Med Assoc, 1937, *cix*, 402
- 29 TOOMEY, J A Ingestion of vitamins A, B, C and D and poliomyelitis, Am Jr Dis Child, 1937, *liii*, 1202
- 30 HUDSON, N P, LENNETTE, E H, and GORDON, F B Factors of resistance in experimental poliomyelitis with comments on immunity in poliomyelitis, Jr Am Med Assoc, 1936, *cvi*, 2037
- 31 LENNETTE, E H, and HUDSON, N P Failure to infect monkeys with poliomyelitis virus through isolated intestinal loops, Jr Infect Dis, 1936, *lviii*, 10
- 32 FABER, H K Acute poliomyelitis as a primary disease of the central nervous system, Medicine, 1933, *xi*, 83

- 33 FLENNER, S Respiratory versus gastro-intestinal infection in poliomyelitis, Jr Exper Med, 1936, lvi, 209
- 34 International Committee for the Study of Infantile Paralysis, 1931, Williams and Wilkins Company, Baltimore, p 73
- 35 BURROWS, M T Is poliomyelitis a disease of the lymphatic system? Arch Int Med, 1931, xlviii, 33
- 36 LANDON, J F, and SMITH, L W Poliomyelitis Based on a study of the 1931 epidemic in New York City, 1934, MacMillan Company, New York, p 39
- 37 DUNNING, H S, and FURTH, J Studies on the relation between microglia, histiocytes and monocytes, Am Jr Path, 1935, xi, 895
- 38 BRODIE, M, and PARK, W H Active immunization against poliomyelitis, Trans Fourth Annual Meeting, Southern Branch of Am Publ Health Assoc, 1935, p 71
- 39 KOLMER, J A An improved method of preparing the Kolmer poliomyelitis vaccine, Am Jr Publ Health, 1936, xxvi, 149
- 40 KOLMER, J A, and RULE, A M A successful method for vaccination against acute anterior poliomyelitis preliminary report, Am Jr Med Sci, 1934, clxxviii, 510
- 41 KOLMER, J A, KLUGH, G F, and RULE, A M A successful method for vaccination against acute anterior poliomyelitis further report, Jr Am Med Assoc, 1935, civ, 456
- 42 KOLMER, J A, and RULE, A M Active immunization against acute anterior poliomyelitis with ricinoleated vaccine, Jr Immunol, 1937, xxxii, 341
- 43 KOLMER, J A Susceptibility and immunity in relation to vaccination in acute anterior poliomyelitis, Jr Am Med Assoc, 1935, cv, 1956
- 44 KOLMER, J A Vaccination against acute anterior poliomyelitis, Am Jr Pub Health, 1936, xxvi, 126
- 45 LEAKE, J P Poliomyelitis following vaccination against the disease, Jr Am Med Assoc, 1935, cv, 2152
- 46 BURNET, F M, and MACNAMARA, J Immunological differences between strains of poliomyelitis virus, Brit Jr Exper Path, 1931, xii, 57
- 47 WEYER, E R Immunological differences between a strain of monkey virus and human poliomyelitis virus, Proc Soc Exper Biol and Med, 1931, xxxix, 289
- 48 PAUL, J R, and TRASK, J D Strains of poliomyelitis virus, Jr Exper Med, 1937, lviii, 513
- 49 TRASK, J D, PAUL, J R, BEEBE, A R, and GERMAN, W J Viruses of poliomyelitis, immunologic comparisons of six strains, Jr Exper Med, 1937, lvi, 687
- 50 KESSEL, J F, STIMPERT, F D, and FISK, R T Studies with poliomyelitis virus II Immunologic comparison of a Los Angeles strain of virus with the M V strain, Jr Bacteriol, 1938, xxxv, 42
- 51 STILL, G F Second attacks of acute poliomyelitis and the minimal duration of immunity, Arch Dis Child, 1930, v, 295
- 52 QUIGLEY, T B Second attacks of poliomyelitis Review of the literature and report of a case, Jr Am Med Assoc, 1934, cii, 752
- 53 FISCHER, A E, and STILLERMAN, M Does an attack of acute anterior poliomyelitis confer adequate immunity? Jr Am Med Assoc, 1938, cx, 569
- 54 SCHULTZ, E W, and GEBHARDT, L P Observations on the prophylactic value of specific immune serum in experimental poliomyelitis, Jr Pediat, 1935, vii, 332
- 55 OLITSKY, P K, and COV, H R Experiments on active immunization against experimental poliomyelitis, Jr Exper Med, 1936, lvi, 109
- 56 KOLMER, J A Antibody in relation to immunity in acute anterior poliomyelitis, Jr Immunol, 1936, xxxi, 119
- 57 HARMON, P H, and HARKINS, H N The significance of neutralizing substances in resistance and recovery from poliomyelitis, Jr Am Med Assoc, 1936, cvii, 552
- 58 HARMON, P H, and HARKINS, H N Occurrence of virucidal substances in patients

- with poliomyelitis bearing on serum treatment and vaccination, Illinois Med Jr, 1936, September
- 59 KOLMER, J A, and RULE, A M Tests for immunity to acute anterior poliomyelitis The technic and status of the monkey serum neutralization or antiviral test, Jr Immunol, 1935, *xxv*, 175
- 60 HARMON, P H, HARRISON, J A, and KERNWEIN, G Skin tests for sensitivity to virus of poliomyelitis, Proc Soc Exper Biol and Med, 1933, *xxx*, 1134
- 61 SABIN, A B, PARK, W H, and JUNGBLUT, C W Nature of skin reactions produced by heat inactivated poliomyelitis virus, Arch Int Med, 1933, *li*, 878
- 62 KOLMER, J A, KLUGH, G, and RULE, A M Tests for immunity to acute anterior poliomyelitis skin reactions to virus, Jr Immunol, 1935, *xxv*, 191
- 63 KOLMER, J A, and RULE, A M Tests for immunity to acute anterior poliomyelitis colloidal gold, complement fixation and precipitation tests, Jr Immunol, 1935, *xxv*, 199

A STUDY OF THE CHANGES IN SERUM CHOLESTEROL, GASTRIC SECRETION AND CARBOHYDRATE METABOLISM IN PATIENTS WITH TOXIC GOITER

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IN 1922, Epstein and Lande¹ studied the blood cholesterol of 24 patients, 14 of whom had exophthalmic goiter and 10 of whom had toxic nodular goiter. The conclusion from this group was that, in general, the decrease in blood cholesterol bears a direct relationship to the extent of increase of the basal metabolic rate. In nine of the 14 cases this was true. The lowest basal metabolic rate of plus 14 corresponded to a blood cholesterol of 196 mg per 100 c c, and the highest basal rate of plus 82 to a cholesterol of 90 mg. However, in this group the relationship was not invariable. In the toxic nodular group of 10 the relationship of the basal metabolic rate and cholesterol was not nearly as definite. Gardner and Gainsborough² in 1928 studied the serum cholesterol in 14 toxic cases and found no evidence to support the belief of an inverse relationship between the cholesterol and basal metabolic rate in hyperthyroidism. Mason, Hunt, and Hurxthal³ found an average blood cholesterol value of 130 mg per 100 c c in 47 patients with toxic goiter whose average basal metabolic rate was plus 57. Hurxthal⁴ reported average cholesterol values in patients with toxic nodular goiter below the normal range and still lower values in patients with exophthalmic goiter. The lowest values occurred in patients in or near thyroid crisis, the next lowest in patients with auricular fibrillation. Later Hurxthal⁵ found that after surgical treatment the blood cholesterol increased as much in patients with exophthalmic goiter as in those with toxic adenomatous goiter.

We determined the serum cholesterol of 50 patients with hyperthyroidism, 18 of whom had exophthalmic goiter with an average basal metabolic rate of plus 56, and 32 of whom had toxic nodular goiter with an average basal metabolic rate of plus 35. The serum cholesterol determination was done by the method of Forbes and Irving⁶. The majority of the patients had received some iodine prior to admission. In the exophthalmic group the cholesterol values ranged from 200 to 67 mg per 100 c c, the high cholesterol value corresponding to a basal metabolic rate of plus 21 and the low to a basal metabolic rate of plus 80. The average cholesterol for this group was 136 mg per 100 c c (chart 1). In a recheck of these same 18 patients in a period varying from 4 to 18 months after operation we

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found the average blood cholesterol to be 190 mg per 100 c c with an average basal metabolic rate of plus 11. There was an increase in blood cholesterol value in all except two patients. These two were only mildly toxic before operation and were free of symptoms when rechecked. In three patients, on whom thyroidectomy was done in stages, some interesting changes were seen in these values. In the case of a 17 year old girl, a cholesterol of 108 mg per 100 c c occurred with a basal metabolic rate of plus 55. A hemithyroidectomy was done and four months later the cholesterol value was 145 mg per 100 c c with a basal metabolic rate of a plus 12. At this time the other side was operated upon. A check on this patient four months after the last operation showed a cholesterol value of 175 mg per 100 c c with a basal metabolic rate of a minus 22. Another, a male 24

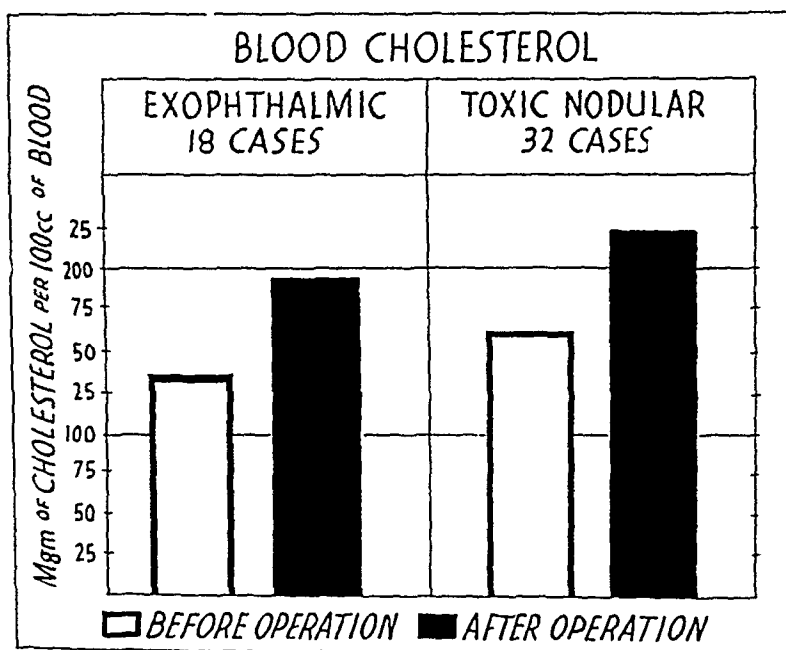


CHART 1

years of age, had a cholesterol value of 90 mg per 100 c c with a basal metabolic rate of plus 85. Two months after a hemithyroidectomy the cholesterol value was 67 mg per 100 c c with a basal metabolic rate of plus 80. The cholesterol value four months after the second operation was 132 mg per 100 c c with a basal metabolic rate of minus 17. The third, a male aged 50, had a cholesterol of 132 mg per 100 c c with a basal metabolic rate of plus 53. A hemithyroidectomy was done and a study six months later showed a cholesterol value of 115 mg per 100 c c with a basal metabolic rate of plus 77. A study six months after the second operation showed a cholesterol value of 202 mg per 100 c c with a basal metabolic rate of plus 37. One patient, a female aged 45, was admitted in a severe thyroid crisis. Her cholesterol value at this time was 144 mg per 100 c c with a

basal metabolic rate of plus 58 The patient refused operation and a study two months later showed a cholesterol value of 167 mg per 100 c c with a basal metabolic rate of plus 42 At this time the patient had a sub-total thyroidectomy and a check 10 months from the time of operation showed a cholesterol value of 188 mg per 100 c c with a basal metabolic rate of plus 10

In the group of 32 patients with toxic nodular goiter the average cholesterol value before operation was 159 mg per 100 c c, and after operation the average was 224 mg (chart 1) All cases except three showed a definite increase after operation The cholesterol values of the three which did not show an increase were nearly the same as before operation

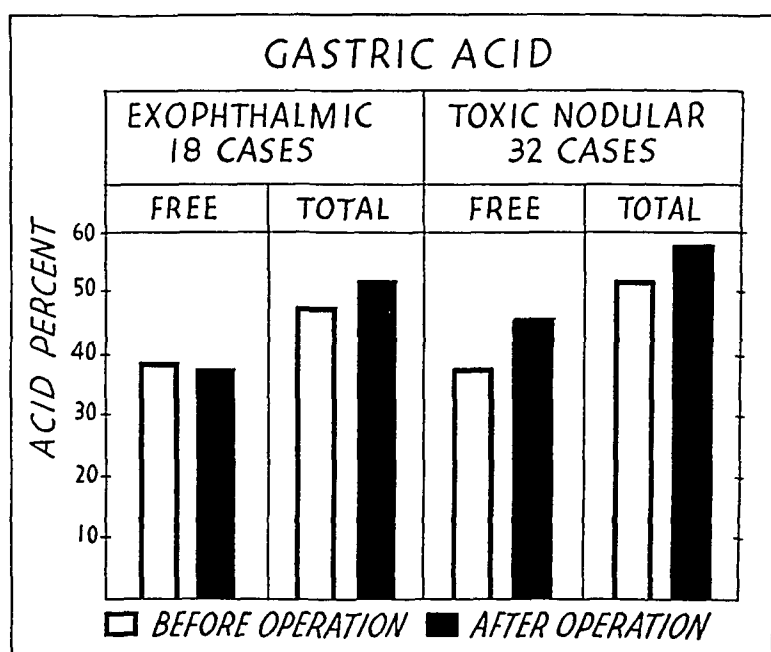


CHART 2

The inverse relationship between the blood cholesterol and basal metabolic rate was not definite by any means in either of these groups, however, there was some tendency for this in the exophthalmic group There was no tendency for an inverse relationship in the toxic nodular group (charts 3 and 4)

Several workers have reported a low gastric acidity and an increased incidence of anacidity in hyperthyroidism but the results were obtained by such test meals as Ewald and not by histamine stimulation Lerman, Pierce, and Brogan⁷ using 50 c c of 7 per cent alcohol as a test meal and 0.5 mg of histamine injected subcutaneously, determined the acid value in 200 normals, distributed fairly evenly between the ages of 20 and 69, as follows free acid 40.4 c c of N/10 HCl for 100 c c and total acid approximately 10

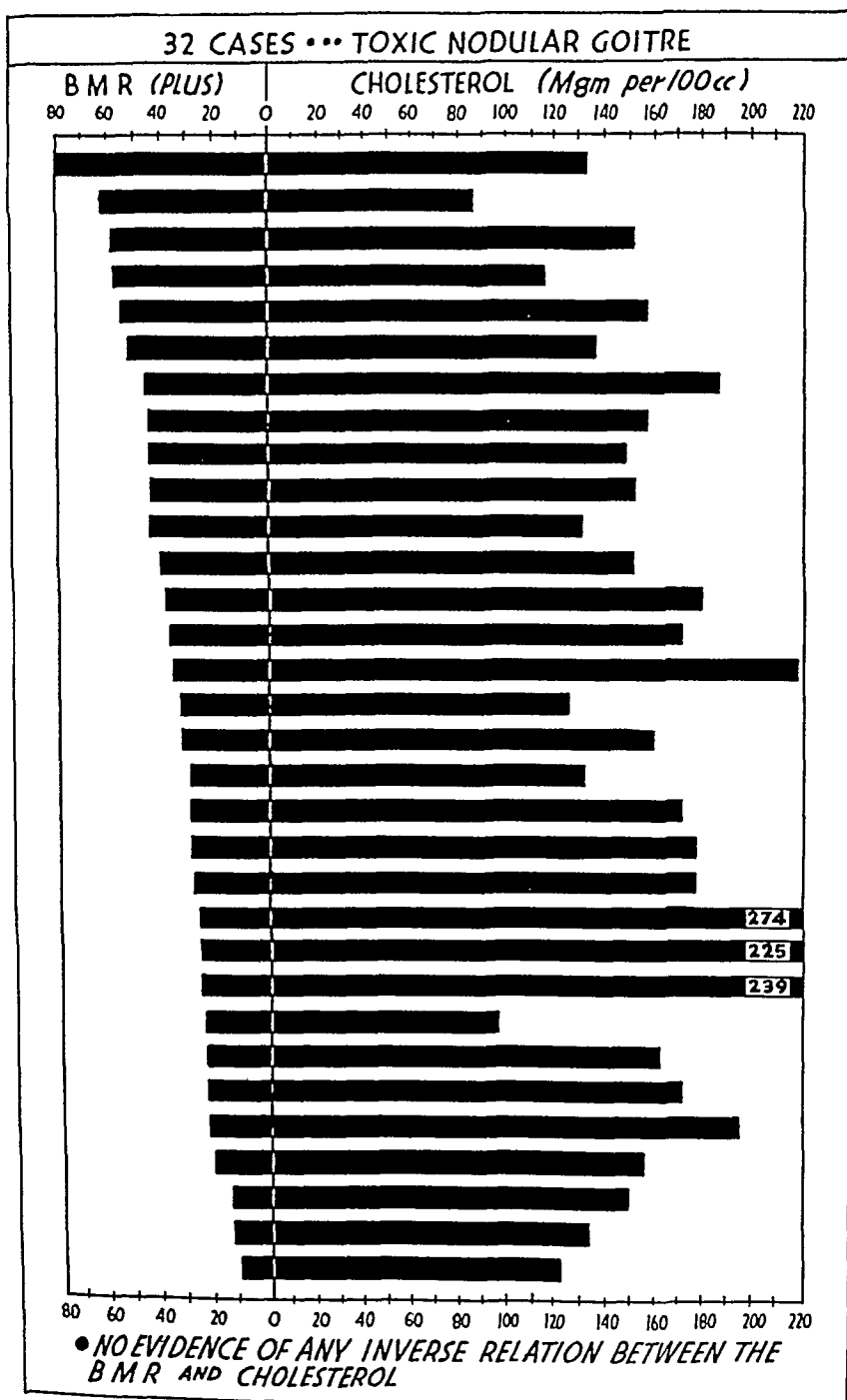


CHART 3

points more They reported an incidence of 13 per cent anacidity, 16.5 per cent hypoacidity, 49.5 per cent normal acidity, and 21 per cent hyperacidity In 50 patients with exophthalmic goiter Leiman and Means⁸ found an anacidity of 38 per cent with a definite tendency to hypoacidity Wilkinson,⁹ using a test meal of 50 c c of 7 per cent alcohol and 0.1 mg of histamine subcutaneously for each 10 kg of weight, found the average free acid in patients with toxic goiter to be 24 c c and total acid 36.9 c c of N/10 HCl for 100 c c In this study there was an anacidity in 36 per cent He

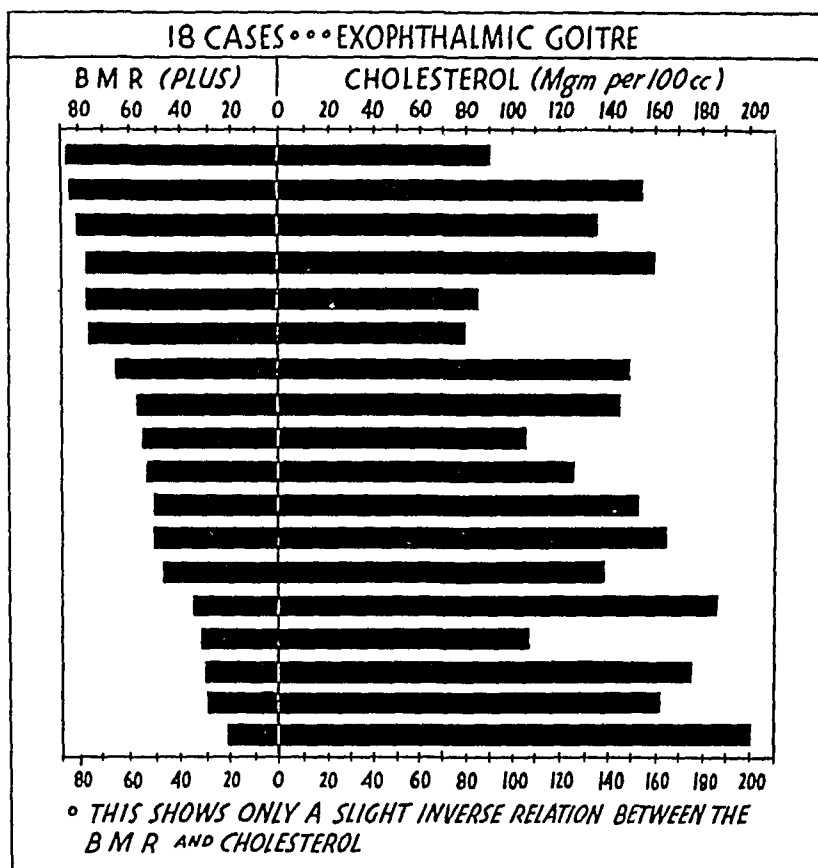


CHART 4

studied 114 cases three months or longer after operation and found an anacidity of only 10.5 per cent The average free acid after operation was 46 c c of N/10 HCl for 100 c c He was able to recheck 25 of the patients who showed achlorhydria before operation and found that 22 of the 25 had regained free acid The average duration of symptoms before operation was 9.2 months in the entire group, whereas in the group that there was no free acid the average duration of symptoms was 16.6 months He suggests that the development of achlorhydria depends on the duration rather than the degree of toxicity

Our gastric analyses were done with the test meal of 200 cc of 7 per cent alcohol and subcutaneous injection of 0.5 mg histamine in the male and 0.2 mg in the female. The stomach contents were aspirated every 15 minutes for one hour. The unit used to express the acid is the maximal cc of N/10 HCl of 100 cc obtained in any one specimen. In the 18 patients with exophthalmic goiter the ages varied from 17 to 56 with a fairly even distribution. The average free acid before operation was 39.3 with a total of 47.2, the average free acid four to 18 months after operation was 38.2 with a total acid of 52.2 (chart 2). Four of these 18, or 22 per cent had no free acid, on the recheck three of the same showed no free acid while

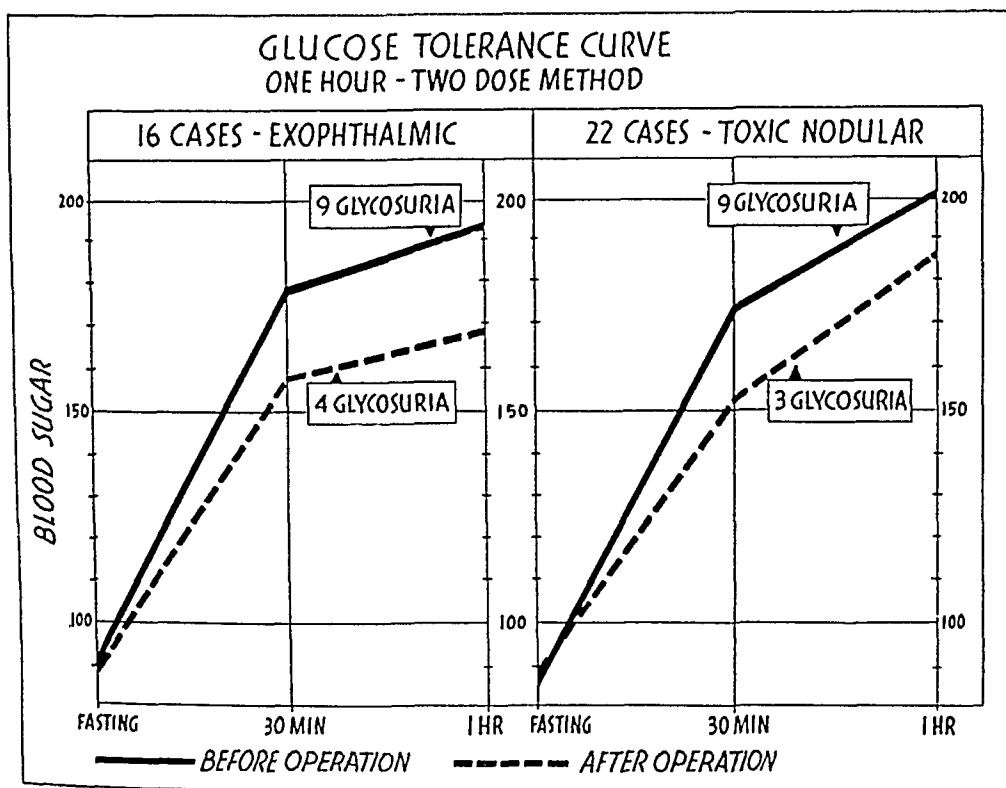


CHART 5

one showed 20. The average length of duration of the toxic symptoms in this group was 30 months, whereas the average length of duration of the toxic symptoms of the four who had no free acid was 33 months. There was no definite relationship between the toxicity and the degree of acidity.

In the 32 patients with toxic nodular goiter the average free acid before operation was 37.3 with a total of 51.5. The recheck after operation showed an average free acid of 46.7 with a total of 58.5 (chart 2). Before operation there were two patients or 6.3 per cent who showed achlorhydria and the same two did not have any free acid when rechecked. However, there was one on the recheck that had an anacidity which had a free acid of

22 before a thyroidectomy. The age of these patients ranged from 24 years to 62 with a fairly even distribution in the various age groups. The average duration of toxic symptoms in this group was 25 months, whereas the duration was 24 and 36 months in the two patients with no free acid.

This series of 50 patients with toxic goiter showed six cases or 12 per cent anacidity before operation with exactly the same after operation. The incidence of achlorhydria in the exophthalmic group was somewhat above the figure given for normal but the occurrence of anacidity in the toxic nodular group was less than that given for normal.

In hyperthyroidism there is impairment in carbohydrate metabolism as determined by the glucose tolerance test and glycosuria. Geyelin¹⁰ studied the glucose tolerance in 27 cases of hyperthyroidism. When he compared the findings with normals he concluded that there is a slowed return to fasting blood sugar value after doses of glucose, and that this is more marked in proportion to the severity of the case. John¹¹ studied 82 patients with hyperthyroidism and 10 of colloid goiter. He found a decreased glucose tolerance curve in 66 per cent and glycosuria in 19 per cent. These were selected cases of hyperthyroidism and do not represent the average incidence of impaired carbohydrate metabolism. In this series there was no relationship between the degree of impairment and the severity of the disease. John¹² later reported his findings of the glucose tolerance curve on 239 cases of hyperthyroidism. These were also selected patients and showed within 1½, the same percentage with glucose tolerance impairment, as the previous 82 cases. Gardner-Hill, Brett, and Smith¹³ studied the glucose tolerance in four patients with severe exophthalmic goiter and found a decreased tolerance and glycosuria in each instance. Wilder and Sansum¹⁴ studied the glucose tolerance of five patients with exophthalmic goiter and found it decreased in each case.

Our studies of carbohydrate metabolism were done by the one hour, two dose glucose tolerance test as described by Exton and Rose¹⁵. The criteria that are given as normal are: A fasting blood sugar within the normal limits of the particular blood sugar method employed, a rise in the blood sugar which does not exceed 75 mg. in the 30 minute sample, the blood sugar in the 60 minute sample is less, the same, or does not exceed the 30 minute sample by more than 5 mg., all urine samples are negative to Benedict's test. It seemed to us after several tests on normal individuals that these criteria are not met, so we have made no attempt to compare our curves with that given by Exton and Rose, but have compared the preoperative curve with that determined several months after operation. The patients who were diabetics were not included in this study. In the exophthalmic group of 18 we had a preoperative glucose tolerance study of 16, and a postoperative study in the same 16. Before operation the average glucose tolerance curve showed a fasting blood sugar of 92.5 mg. per 100 c.c., at the end of the one-half hour 179.3 mg., and at the end of the hour 192.8 mg. Nine or 56.2 per cent of these 16 showed glycosuria at the end of the hour. Several

months after operation the average fasting blood sugar was 90.8 mg, at the end of the one-half hour 157.8 mg, and at the end of the hour 168.9 mg (chart 5). Four patients or 22 per cent showed glycosuria, three of which showed glycosuria before operation and one did not. There was no definite relationship between the degree of toxicity and the decrease in carbohydrate metabolism. The patient admitted in crisis showed a fasting blood sugar of 110 mg per 100 c.c., 258 mg at the end of the one-half hour, and 207 mg at the end of the hour. Some sugar was found in the urine specimen at the end of the hour. Recheck several months after the crisis showed a fasting blood sugar of 92 mg per 100 c.c., 194 mg at the end of the one-half hour, and 260 mg at the end of the hour. The urine specimen at the end of the hour contained sugar. Several months after this patient had a subtotal thyroidectomy her fasting blood sugar was 90 mg per 100 c.c., 156 mg at the one-half hour, and 126 mg at the end of the hour. There was no glycosuria.

In the toxic nodular group we had preoperative and postoperative carbohydrate metabolism studies in 22 patients. The average curve before operation showed a fasting blood sugar of 85.9 mg per 100 c.c., 173.5 mg at the end of the one-half hour, and 201.1 mg at the end of the hour. There were 9 or 40.9 per cent that had glycosuria at the end of the hour. After operation the average fasting blood sugar was 89.8 mg per 100 c.c., at the end of the one-half hour 152.4 mg and at the end of the hour 185.6 mg (chart 5). There were three patients or 13.6 per cent who showed glycosuria, two of whom had glycosuria before operation and one did not.

SUMMARY AND CONCLUSIONS

1 While there is a general tendency for the cholesterol values to be low in patients suffering from hyperthyroidism, we could demonstrate no definite inverse relationship between the degree of toxicity as measured by the basal metabolic rate and serum cholesterol level. In patients with exophthalmic goiter there is only a slight tendency toward an inverse relationship between the degree of toxicity as measured by the basal metabolic rate and level of the serum cholesterol. In patients suffering with toxic nodular goiter this tendency was not evident. Generally speaking, the cholesterol values were definitely higher after operation, the degree of increase being essentially the same in the two groups.

2 Acid figures obtained in this study as to the frequency of anacidity do not agree with those of Lerman and Means and Wilkinson, although this is a smaller group. There was no relationship between the degree of toxicity and the amount of acid. The incidence of anacidity in this group before and after operation was 12 per cent. The average free acid in the exophthalmic patients was slightly less after operation, while in the 32 patients with toxic nodular goiter it was increased somewhat.

3 There was frequently an improvement in carbohydrate metabolism after operation as measured by the glucose tolerance curve and glycosuria.

BIBLIOGRAPHY

- 1 EPSTEIN, A A , and LANDE, H Studies on blood lipoids, the relationship of cholesterol and protein deficiency to basal metabolism, Arch Int Med, 1922, xxx, 563-577
- 2 GARDNER, J A , and GAINSBOROUGH, H The relationship of plasma cholesterol and basal metabolism, Brit Med Jr, 1928, ii, 935-937
- 3 MASON, R L , HUNT, H M , and HURATHAL, L M Blood cholesterol values in hyperthyroidism and hypothyroidism—their significance, New England Jr Med, 1930, cciii, 1273-1278
- 4 HURATHAL, L M Blood cholesterol in thyroid disease, analysis of findings in toxic and non-toxic goitres before treatment, Arch Int Med, 1932, li, 22-32
- 5 HURATHAL, L M Blood cholesterol in thyroid disease, effect of treatment, Arch Int Med, 1933, lii, 86-95
- 6 FORBES, J C , and IRVING The determination of cholesterol in whole blood, Jr Lab and Clin Med, 1930, xvi, 909-912
- 7 LERMAN, J , PIERCE, F D , and BROGAN, A J Gastric acidity in normal individuals, Jr Clin Invest, 1932, xi, 155-165
- 8 LERMAN, J , and MEANS, J H Gastric secretion in exophthalmic goitre and myxedema, Jr Clin Invest, 1932, xi, 167-182
- 9 WILKINSON, S A Gastric acidity in thyroid dysfunction, Jr Am Med Assoc, 1922, ci, 2,097-2,099
- 10 GEYELIN, H R The carbohydrate metabolism in hyperthyroidism as determined by examination of blood and urine, Arch Int Med, 1915, vi, 975-988
- 11 JOHN, H J Carbohydrate metabolism in hyperthyroidism, Endocrinology, 1917, vi, 497-578
- 12 JOHN, H J A study of 1,100 glucose tolerance tests, Med Jr and Rec, 1930, cxvii, 287
- 13 GARDNER-HILL, B H , BRETT, P C , and SMITH, J F Carbohydrate metabolism in myxedema, Quart Jr Med, 1925, viii, 327-334
- 14 WILDER, R M , and SANBURN, W D Glucose tolerance in health and disease, Arch Int Med, 1917, ix, 310-334
- 15 EATON, W G , and ROSE, A R The one hour two-dose dextrose tolerance test, Am Jr Clin Path, 1934, iv, 381-399

TRENDS IN PUBLIC HEALTH¹

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PUBLIC health is one of the newest and the most rapidly growing specialties of medicine. This has been due to a number of factors among which are

1 The growth of scientific medical knowledge makes possible effective means of prevention and treatment for an increasing number of diseases

2 The increasing concern of man for the well-being of his fellow man. This growth in the sentiment against suffering, as Newsholme calls it, has found expression in a large structure of social laws, the effort to provide more nearly adequate measures of relief for the destitute, unemployment insurance, and many other enactments

3 The transition from an agrarian to an industrial economy has increased the interdependence of the population. An industrial civilization with workers dependent upon a daily wage leaves them more exposed to the risks of dependency. They are victimized by the play of economic forces beyond the power of the individual to control

4 Good health is a factor in physical efficiency, therefore in national efficiency. Conversely, the ill health of individual citizens lowers the nation's fitness, lessens its chance of survival in a warring world, and depletes city, state and federal budgets

If medicine were a static or a decadent science, public health—which means putting medicine to work for the whole people—would stand still or regress. On the contrary, medicine, as we all know, is perhaps the most dynamic of the sciences. Public health action, through which the beneficence of medicine is canalized for the common good, should keep abreast of medical advances

Formerly the rich had good medical care as a privilege. During the last generation the poor in some cities have had it as a matter of charity. We now have reached a stage in the evolution of citizenship when all the people, poor and rich alike, are beginning to demand at least a minimum of health protection as a right. Our plans for distributing such health protection must be based on the concept of an equal opportunity to be born healthful, to maintain health, to prevent needless disease, unnecessary disablement, and premature death. To the informed modern mind, this opportunity for health is beginning to rank with the other basic equalities of American life—freedom of speech, of faith, of assembly, of franchise. No man can fully exercise his rights and privileges if he has not also the inalienable privilege of health. There is no citizen, however patriotic, but is embittered if he knows that to some are given the privileges of healthful living while to him they are denied

* Read at the New York meeting of the American College of Physicians, April 4, 1938

Those of us who practice the specialty of public health accept as our major function the application to mass health of life saving methods worked out with endless patience in the research laboratory, at the bedside, and in the field. It follows that each accretion to our present knowledge both of prevention and the cure of disease extends the scope of public health.

A corollary of the growth of medical knowledge is that it increases the cost of applying the sum total of that knowledge for the benefit of the patient. This means that good medical care is beyond the reach of an increasing number of persons, for the treatment of disease increasingly calls for coordination of many technics, facilities, and the collaborative wisdom of many specialists.

In an earlier day the problem was simple. The health officer did what he could to prevent disease, chiefly through sanitation and quarantine measures. On the other hand, the family doctor could carry in his head most of the medical knowledge of the day and in his little black bag most of the ways and means of using it. That day has passed. Yearly we are confronted with a larger list of diseases which can be prevented in the community as a whole if sick persons are treated promptly. I need not detail them to this audience. Even the layman knows that this is true of syphilis, of tuberculosis, to a certain extent of cancer and of other diseases which leave a tragic trail of disablement and death. Even the layman knows that a large proportion of infant and maternal deaths are unnecessary.

When medicine was an empirical art and not yet science, it mattered little whether or not the mass of the people had the services of the medicine man and the barber surgeon. Now, however, the community is beginning to concern itself with the prevention, alleviation and cure of all sickness, disability and premature death, just as it protects itself against burglaries, embezzlement, arson, and murder. Both disease and crime are economic waste. By taking the proper precautions, much of both can be prevented from doing serious damage to the community.

Public health services result from community interest in them. Such interest is spontaneous and continued when inspired by good health teaching to show the goal and by medical leadership which is genuinely concerned to work out a method of attaining that goal. Public health, then, embraces the prevention and cure of all diseases which because of their wide prevalence, their serious nature, or their costly treatment cannot be dealt with adequately by the individual efforts of the patient. In addition to the examples I have suggested—syphilis, tuberculosis, and cancer which, in the light of our present knowledge, can be controlled most readily through early treatment of the patient—this definition of prevalence, seriousness or cost may be illustrated further by the care of the insane, which is beyond the financial resources of the average family, the campaign against pneumonia, the after-care of poliomyelitis, the treatment of the disabling chronic diseases, and the provision of all medical care for the dependent groups of the population.

It is also a function of public health to pursue scientific research and investigations which have for their object better methods of preventing and treating those diseases against which our scientific weapons now are not effective.

The changes in the concept and scope of public health have complicated relationships between public and individual efforts to give medical care and to protect health. To my mind, most of the complications are needless. Unfortunately, we have not always maintained the same dispassionate point of view toward these relationships which has characterized our search for truth in the laboratory and at the bedside of the patient. Many of our finest physicians have given little or no attention to the broad problems of disease prevalence and the proved public health methods of dealing with certain diseases. It is equally true that many of our ablest public health administrators have lost touch with the personal problems and the clinical viewpoint of the private practitioner. In viewing the whole status of medicine and public health today, we need to know enough about one another's problems to understand them and to maintain the same scientific and dispassionate attitude which the doctor is taught to use in dealing with disease.

Each individual cell has a part to play in the beautifully adjusted mechanism of the human body. Any dysfunction in a group of cells or an organ of the body brings symptoms in remote parts or in the whole organism. In a comparable manner the unnecessary illness of any person in modern society, or of any group of the population has a direct relationship to the function of the society in which he is a part. The excess of illness among the poor, the lack of good medical care, the continued prevalence of preventable disease, the unnecessary loss of life, all are of importance to society as a whole.

Half of all illness is among the very poor, it has been found in the recent National Health Survey made by the Public Health Service. Twenty-five per cent of all illness is in families on relief, another 25 per cent is among families whose total income is less than \$1,000 a year. It is estimated that more than half a million persons in the United States—and three-quarters of them heads of families—are unemployable because of accident or disease, much of it preventable. Further, 80 per cent of all unemployable heads of families are either on relief or in the group having less than \$1,000 annually. This is a ratio of one in every 20 in the relief and low income classification as compared with one in 250 similarly disabled among those in more comfortable circumstances.

The community pays for preventable disease and disability. It pays in relief of the unemployables, in pensions and in institutional care. It would be cheaper for us as a nation to spend more for the prevention and cure of disease than to continue to bear its money cost. It is, therefore, not only the humane but the practical considerations which bring to our attention the acute need for dealing courageously with unnecessary sickness in this country. Our efforts up to now have been sporadic, half-hearted, and

frequently unscientific. The time seems opportune for the best minds in the medical profession to consider how medical knowledge can best be brought to fuller use by all of the people—how we may take up the lag between what we know and what we do. It should be possible for a national health program to be evolved which would be adapted to the varying needs of each state and community.

A practical program to utilize our scientific resources for life-saving would bring advantages to our profession almost as great as to the population which would be served. Among other things, it would go a long way toward ousting the quacks and cults and unqualified practitioners of medicine. One does not find them in the Scandinavian countries, for example, where medical service is available both to those who can pay well and those who can pay a little and where medical service is so uniformly good as to be universally trusted. Moreover, a well-rounded national health program would solidify the forces of public health and the forces of medical practice which, after all, are but the two useful arms of the greatest of sciences. And finally, such a program would inevitably restore to the medical profession the trust and confidence of all the people, would wipe out the disaffections which have arisen because medicine has been misinterpreted to the people. Our best and greatest leaders in clinical medicine have been modest and reticent. Our wordiest spokesmen have not interpreted the humanities which are the foundations of medicine. They have made it a defensive thing, a trade union. They have failed, in the minds of many lay people, to identify the common good as the first interest of medical organization.

In approaching this problem it is my opinion that we should not continue to think in terms of the separateness of public, private and voluntary efforts to prevent and cure disease. There is an interrelationship, even a unity of the several parts. Whether we consider the doctors, the dentists, the nurses, the pharmacists, the hospitals, the laboratories, the social welfare and relief agencies, or the public health departments, we must realize that each exists because each has a part to play. We need a united effort—a supreme effort from every integrated factor—if we are to bring better health to more of our people.

I would suggest that our objective in part should be more medical care and health service for those unable to procure it for themselves. An equally important objective, however, is constantly to improve the quality of medical care for this and other groups of the population.

Health insurance, per se, does not either prevent disease or improve the quality of care. Its cost bears most heavily upon the small wage-earner least able to pay. The collection of premiums from any except industrial workers is difficult, if not impossible. Health insurance assumes the continued existence of the current volume of illness as unavoidable and merely spreads its cost. Nowhere does it provide for such expensive and long-continued treatment as is needed in tuberculosis and mental disease. Even venereal disease treatment is not included in most existing insurance

schemes. It cannot embrace the groups on relief, because they have nothing to contribute. Public taxes must take the place of insurance contributions for them and must supplement the contributions for the entire low-income group, or else another system must be worked out for their care.

It is for these reasons that I disagree with those who look upon health insurance as a cure-all for our admitted deficiencies in protecting the health of the people. To my mind health insurance in its most successful existing form will make very little impact upon the actual amount of disease in our population. Whether we have health insurance or not makes very little difference, I think, to our great basic problem of saving life and reducing disability.

A line of progress sounder than health insurance has seemed to me to consist of applying the knowledge we now have for the prevention and control of those great causes of disease and death against which there are scientific weapons of unquestioned power. To do this requires no radical revision of medical practice, no standardized program for every township health officer and county medical society. We need only to build better and more wisely in the patterns we now have. We need to mobilize the forces now in the field but with leadership so scattered, with such vagueness of purpose, and diversity of direction as frequently to obstruct state and national progress in health rather than to advance it. I firmly believe that every health organization should have local control and that every health program should be built on the specific needs of the community it is designed to serve. But unless we do have a health organization in every community, unless the leading doctors in each state are interested enough to set its standards and the state health department is competent to supervise it, unless the state has federal leadership and financial assistance as merited, we shall never have a national health effort against the great plagues of our day.

In many areas, particularly the rural areas, there is a serious shortage of hospital and other physical facilities for good health. Many whole states have practically no beds for tuberculosis, and scarcely the beginnings of a case-finding program. Many areas lack essential laboratory facilities. Mental hospitals frequently are only over-crowded warehouses for the storage of the wrecks left by mental disease. There is a shortage of nearly 200,000 general hospital beds, yet through community bad management hospital beds stand empty in many of our cities.

For those on relief and otherwise unable to support themselves, we should substitute for our present haphazard practice of inadequate care, or no care at all except by the generosity of the doctor, a minimum standard of general medical, nursing and hospital service paid from public funds and given as a matter of right and not of charity.

For those in the marginal economic groups we should supplement what they can do for themselves by public aid in providing the expensive diagnostic and treatment services necessary in obscure conditions and catastrophic illness. The same yardstick used in measuring the need of these

underprivileged for food and shelter is not a measure of their ability to provide for sudden, serious illness. The yardstick should be what the individual needs to restore him to health and competency. He should not be degraded by the pauper's oath because sickness has struck him or his family.

Local responsibility and action should be encouraged to the extent that local resources are available. It would seem wise, also, to use federal funds for these purposes to the extent needed to insure minimum standards and to equalize the financial burden between the states.

In such a plan the medical profession itself should be made responsible for prescribing the standards of service and enforcing good professional conduct. There should be a constant effort to improve the quality of medical service. Better financial and professional opportunities are necessary if medicine is to grow as an instrument for public welfare. A grateful public would be anxious that the profession share in the additions to our national income which are inevitable from a more healthful citizenship.

All of these aims are realizable. All can be accomplished without any basic change in our present system of medical practice. The suggestions which I have ventured to make represent no new or untried action. They represent only an extension, on a scale adequate to meet the needs, of methods and actions which now are in operation.

It is true that if the economists were able to show us how to produce and distribute an income adequate for the health and other needs of every family, the need for many of the measures I suggest would be minimized. The inter-relationship between poverty and disease is well known. Disease begets poverty which in turn creates further disease. Our ability to prevent disease far exceeds our ability to control causes of poverty. Medicine and public health, therefore, should lead rather than follow. Its application offers the best opportunity to interrupt the downward spiral, to tear out the roots of poverty and its companion, ignorance, by attacking its one real preventable factor. Medicine can give hope and confidence to an age almost despairing that man's intelligence will keep us from reverting to barbarism.

In these days of international marauders, when force replaces reason, when hate rather than human understanding rules the mind of man, in these days when well-meaning citizens, otherwise rational beings, allow passions and prejudices to dominate even the domestic scene, in these days when the economists and statesmen seem uncertain of what is the clear road ahead, let us, the doctors and the scientists, not sit idly by. We are all aware that for many diseases we have scientific weapons of unquestioned power. Give us the means of using them for every citizen. Give every man or woman born an American an equal birthright of health. The objectives are clear. There is no serious disagreement as to method. Let us admit with equal frankness that for many diseases and conditions we have imperfect knowledge. Give us means to extend it,—freedom to seek the truth and the will to pursue it.

CASE REPORTS

HYPERPARATHYROIDISM WITH RATHER RAPID RECALCIFICATION OF BONE FOLLOWING THE REMOVAL OF AN ADENOMA

By THOMAS P. SPRUNT, M.D., F.A.C.P., *Baltimore, Maryland*

THE body's calcium is obtained of course from the food. Its absorption from the intestinal tract is aided by vitamin D. In the blood stream the amounts of calcium and phosphorus are maintained at the so-called normal steady level as physiological constants by the activity of the parathyroid glands which govern the deposit or the resorption of calcium and phosphorus from the storehouses in the bones. The bones therefore play an important part in the metabolism of these elements in addition to furnishing the rigidity of the skeleton and spaces for the bone marrow or blood building organs.

We have recently become acquainted with the fact that with the growth of a functioning adenoma of parathyroid tissue and the presence of a great excess of this material there may develop a state of chronic hyperparathyroidism, the essential clinical features of which may be described under three general categories. First, there is the excessive withdrawal of calcium from the bone with a demineralization of bone, fibrous replacement and the development of cysts and giant celled tumors or osteoclastomata. There are pains and aches in the body and extremities and perhaps fractures through the cysts or other weakened portions of the bone. Second, the hypercalcemia or excessive amount of calcium in the blood which is associated with a hypophosphatemia may be linked with the muscular hypotonia, relaxation of the joints, flat feet, lassitude, fatigability and malaise. Third, the hypercalciuria, or excessive excretion of calcium in the urine, may result in a polyuria or a tendency to the formation of renal stones and to damage of the kidney itself from calcium deposits in the renal tissues.

It has been demonstrated repeatedly that after the removal of the excess parathyroid tissue by excision of the tumor, the process is reversible and the patient can be cured provided no marked bony deformities have occurred and the kidneys have not been greatly damaged.

The case I have to report presents a number of interesting features.

CASE REPORT

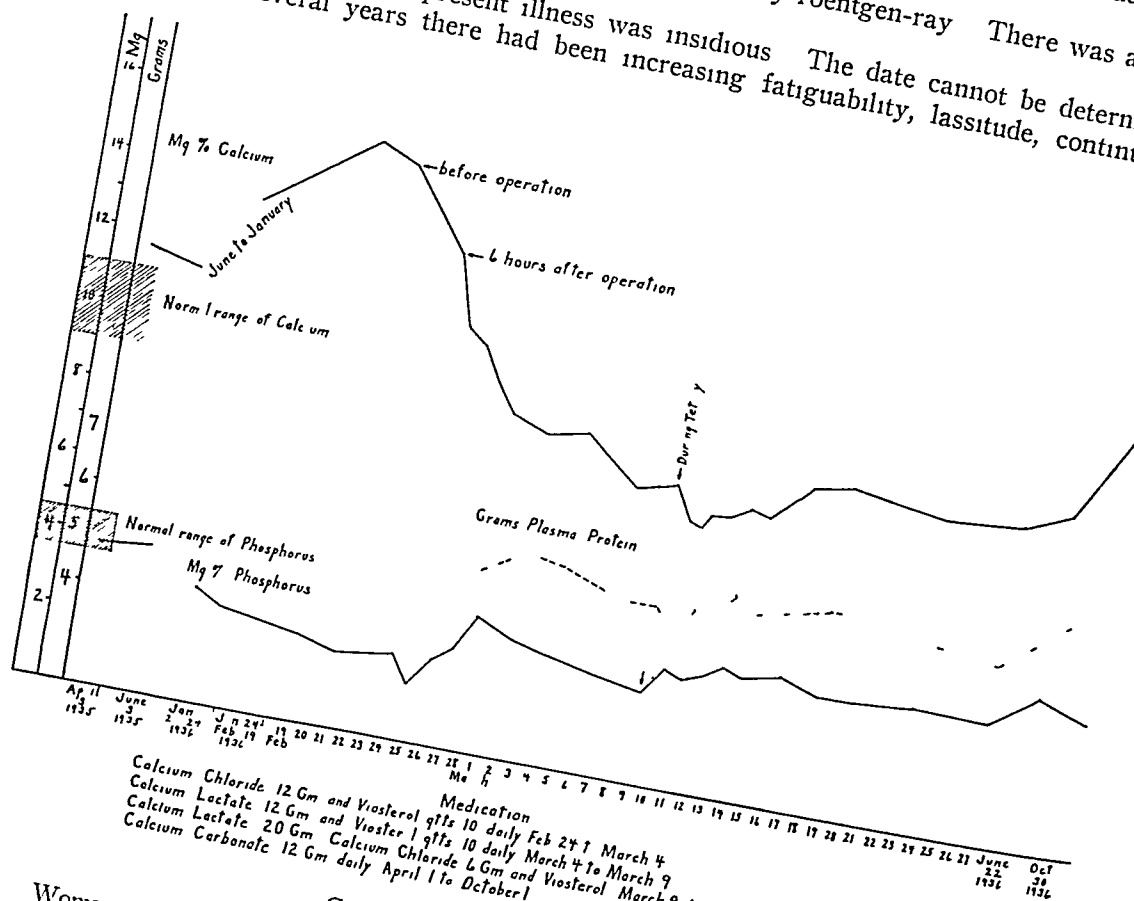
The patient was a woman, 54 years old when we first saw her in April 1935. She had never been robust. She had three children and while nursing the second child, 16 years before, she had suffered an attack of manifest tetany that was satisfactorily treated with calcium. Evidences of latent tetany persisted for some time. We may assume that under conditions demanding unusual amounts of calcium, her food supply was deficient in this element, or perhaps more probably there was a lack of vitamin D resulting in a low blood calcium level and the symptoms of tetany. We

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THOMAS P SPRUNT

have here a satisfactory setting for a more or less prolonged stimulation of the parathyroid apparatus in the effort to compensate for this deficiency. Perhaps, as Wilder assumes, there were cell rests with parathyroid potentialities that received their stimulus to development at this time and later grew into a functioning parathyroid adenoma.

Nine years ago, the menopause was induced by roentgen-ray. There was at this time a sharp but short depression. The date cannot be determined. The onset of the present illness was insidious. The date cannot be determined but for several years there had been increasing fatigability, lassitude, continuous



CASE OF HYPERPARATHYROIDISM

Woman, aged 54 years, complained of aching in hips, legs and knees, stiffness and difficulty in walking, malaise, fatigue. Mother of 3 children. Tetany while nursing second child 16 years ago. "Nervous breakdown" 9 years ago. Increasing disability past few years. Fracture left wrist September, 1933, and again January, 1934.

CHIEF CLINICAL FEATURES

General Hypercalcemia, hypophosphatemia, lassitude, weakness, fatigability, muscular hypotonia.

Bones Pain in chest, knees, feet and legs, flat feet, general rarefaction of bones with cysts or giant celled tumors in skull, ribs, jaw, pelvis, fingers, arm and leg.

Kidneys Mild polyuria, fixed low specific gravity, reduced phthalein excretion, slight arterial hypertension.

Operation (Dr. Rienhoff), February 24, 1936. Removal of parathyroid adenoma 2 cm in diameter.

Postoperative Course Prompt fall in serum calcium, tetany on 15th postoperative day. Slow gradual symptomatic improvement continuing throughout the 8 months. Rather rapid general recalcification of bones and filling in of all local lesions except one phalanx. Dense calcification of lesions after 4 months. More nearly normal bone after 8 months.

aching in the hips, legs and knees with difficulty in walking and stiffness now in the feet and then in the knees. In September 1933, and again in January 1934, there had occurred fractures of the left forearm from falls on the floor in her home. In June of 1934, weakness increased and shakiness began so that she could not knit on account of the tremor. She was comparatively comfortable in bed but was never entirely free from pain. She had been given full doses of thyroid for a period but none since August 1934. She had received a good deal of calcium until October 1934, but none from this time until after the operation 18 months later. Her appetite was poor, she was nervous with occasionally mild depression, but slept well. She was sensitive to cold. There was no constipation.

Physical Examination She was rather tall, five feet, eight inches in height and weighed 136 pounds. Her gait was uncertain, weak and rather awkward. She could not rise from a sitting position in a chair without using her hands to help push the body upward. In the standing position the posture was fairly good with the exception of a slight upper thoracic kyphosis. There was a slight deformity just above the left wrist, the site of fractures some months before. There was no definite tenderness of bones or of joints, which were negative on general physical examination with the exception of mild crepitus in the knee joints. The muscles were flabby and atonic. The neurological examination was negative. The pulse was regular, rate 76. Blood pressure 130 mm of mercury systolic and 90 diastolic. The thyroid gland was palpable with a rather full isthmus and right lateral lobe which was somewhat nodular. The skin was rather dry.

There was a refractive error but otherwise the eyes were normal.

Roentgen-ray examinations showed in the lateral view of the spine some sharpening of the points of the vertebrae and one vertebra near the mid portion of the thoracic spine that was wedge-shaped, suggesting a mild compression fracture. The bones of the thoracic and lumbar portions of the spine and of the pelvis appear somewhat rarefied. Films of the left hand and wrist showed a well healed fracture of both radius and ulnar bones. The lateral view of the skull showed a normal sella turcica. There was no striking rarefaction of the bones of the calvarium. Films of the teeth were not remarkable.

Laboratory Tests The basal metabolic rate was retarded, minus 17 per cent, minus 20 per cent. There was a moderate secondary anemia with red blood cells 4,000,000, hemoglobin 70 to 75 per cent, white blood cells 8,300 with a normal differential count. The blood Wassermann reaction was negative. Stools were normal. The urine showed a rather low specific gravity, 1.008 to 1.010, with a trace of albumin and very few casts. The gastric analysis and examination of the cerebrospinal fluid had been done elsewhere and were normal. Chemical tests of the blood revealed a fasting blood sugar of 98 mg per cent, non-protein nitrogen 32.5 mg per cent, blood uric acid 4.7 mg per cent, blood calcium 11.6 mg per cent, and blood phosphorus 3.8 mg per cent.

The diagnosis of hyperparathyroidism was not made at this time. The rarefaction of the bones was enough to be noticed in an objective description of the roentgen-ray films but was not marked. The blood chemistry was practically normal. The value for calcium at 11.6 mg per cent may be considered a little high but the phosphorus at 3.8 mg per cent was quite normal. The patient remained under our observation from April 12, 1935, to June 23, 1935, with a general rest and upbuilding plan of treatment, during which she gained 20 pounds in weight but only slightly in strength and feeling of well-being. The blood counts at times were as low as 3,700,000 red blood cells and 70 per cent hemoglobin, and this secondary anemia did not respond favorably to treatment until after large doses of iron and of liver had been given. From one to two grains of thyroid were given each day and the basal metabolic rate increased to the lower levels of normal. Roentgen-ray films of the bones in June showed no striking changes from those taken previously. The blood

calcium at the end of this period was 11.2 mg per cent and the blood phosphorus 3.9 mg per cent, practically normal values

We saw the patient again on January 20, 1936. There had been no great change in her symptoms. She felt that in some respects she was a little better but the aching was as severe and although she walked better, she found it difficult to get up from a chair and the discomfort in the knees was worse. Fatiguability and lassitude persisted. She was very nervous and at times quite weepy. She gave the additional interesting history that in September of 1935 an operation had been performed for a cyst of the jaw by which she had lost three teeth.

The physical examination was quite similar to that of 10 months before. The height was the same, 5 feet, 8 inches, and the weight 143 pounds. The blood pressure had increased to 150 systolic and 90 diastolic. The gait was about the same as before. The musculature of the legs seemed generally weak and she spoke of a feeling of insecurity about the left wrist.

The roentgen-ray films taken at this time and others taken a month later were quite illuminating.

The thoracic and lumbar portions of the spine showed no striking changes from the films of the year before except perhaps for some increase in the decalcification. The film of the pelvis showed definitely increased general rarefaction of the bones and this was particularly striking in the cancellous portion of the upper third of each femur. In the left ischium there was a very distinct round clear area that measured about $1\frac{1}{2}$ by 1 cm. There were other less definite localized cyst-like areas, one in each ilium and one in the head of the right femur.

The ribs and clavicles in general were moderately rarefied and there were large fusiform lesions, one on the seventh right rib and another on the ninth left rib. There were other small, less sharply defined localized areas of rarefaction in the ribs and the upper ribs on each side showed a moth-eaten appearance of the outer border particularly on the superior surface.

Other films of the chest and of the pelvis the following month showed little change during this period. Roentgen-ray films of the arms in February showed the long bones distinctly rarefied with rather thin cortex and porous cancellous portions. Just above the site of the old fracture of the left wrist there was in the left ulna a large lesion expanding the outlines of the bone and with a very thin cortex around it. This lesion measured about 5 by $1\frac{1}{2}$ cm and was crossed by bony trabeculae.

The bones of the hands showed increased radiability. The phalanges of the right fore-finger showed the only localized lesion. The middle phalanx was a mere shell with a very thin cortex around it. The distal portion of the proximal phalanx contained a cyst-like area which measured 1 cm by 8 mm. A film of the left shoulder showed rarefaction in the humerus, in the scapula and in the clavicle as well as in the ribs. The lateral view of the skull taken in February showed a fine mottling involving the bones of the whole calvarium. There were three small clear cyst-like areas in the parietal region, one of them about 1 cm in diameter and the other two slightly smaller. The tables of the skull appeared a little broad in the fronto-parietal region.

The femora showed no marked changes except near the ends of the bones where the general rarefaction was noticeable. The tibiae showed a certain degree of general rarefaction as well as the fibulae. There was a small sub-cortical clear cyst-like area in the right tibia surrounded by an area of increased density. A hand's breadth above the ankle the left tibia showed a thin cyst-like area, apparently in the cortex in the anterior portion of the bone. This was long and narrow, measuring about 2 cm by 5 mm. The bones of the feet showed general rarefaction but no localized lesions.

Roentgen-ray films of the kidneys showed that the kidney shadows were of normal size and in normal position. There was no suggestion of a stone in the

region of the pelves, ureters or bladder. There was no definite calcification in the region of the kidneys with the possible exception of one small speck about the size of a pin head in the left kidney.

Laboratory Tests The basal metabolic rate was approximately the same as ten months previously, minus 18 per cent, minus 19 per cent, although the patient had continued to take a one grain tablet of thyroid daily.

The blood count was now normal. Stool examination negative. Urine showed low specific gravity, a trace of albumin and a few casts.

The blood calcium was 13.2 mg per cent and the blood phosphorus 3 mg per cent. A repetition of this test a few days later showed the calcium 13.7 mg per cent and the phosphorus 2.7 mg per cent. Further studies of the urine showed a mild polyuria with an output of about two liters a day, with low fixed specific gravity and a slightly reduced phenolsulphonephthalein output, 35 per cent in two hours. Tests for Bence-Jones proteinuria were negative. The non-protein nitrogen of the blood was normal.

The diagnosis of hyperparathyroidism was now clear and the patient readily consented to an exploration of the parathyroid region in the hope that a tumor might be found and removed.

In summary there were (1) a typical picture of *ostitis fibrosa cystica* with generalized rarefaction of bones, with definite evidence of cysts or giant celled tumors in the skull, ribs, ulna, phalanges, pelvis, femur and tibiae. There was the history of a cyst of the jaw having been treated a few months before and of two fractures of the left arm two years or more ago. There were pains and aches in the bones and soft parts.

(2) There was definite hypercalcemia, the calcium reaching 15.2 mg per cent before the operation, definite hypophosphatemia with a value of 2.3 and later 2 mg per cent. Associated with these features were the weakness, lassitude, fatigability and muscular hypotonia.

(3) There were signs of a renal disturbance in the mild polyuria, with urine of low specific gravity, trace of albumin and a few casts, reduced phenolsulphonephthalein output, but no evidence in the roentgenograms of calcification of the kidney nor of renal stone.

The operation was performed on February 24, 1936, by Dr. William F. Rienhoff, Jr. On lifting the left lobe of the thyroid gland there was found behind it a round mass, 2 cm in diameter, gray in color, smooth and soft, attached by separate blood supply but loosely to the lower pole of the thyroid gland. This tumor was removed with the exception of a small portion that was left in situ and another small piece that was imbedded in the sternocleidomastoid muscle, in order to minimize the danger of postoperative tetany.

Subsequent histological examination of the mass showed a very cellular tumor, the cells quite uniform in size and of polyhedral shape. The nuclei were round or ovoid with evenly dispersed chromatin granules. The nuclei varied only slightly in size but there were a few giant forms. No mitotic figures were noted.

Postoperative Course The output of urine decreased from 2,000 cc the day before operation to 350 cc the day after operation. Subsequently the amount of urine gradually increased until three or four weeks following the operation it had reached almost three liters a day, a figure distinctly higher than the pre-operative level. The specific gravity remained low but the phthalein excretion at this time was 50 per cent in two hours.

The blood calcium fell promptly. On the evening of the operative day it was 12.8 mg per cent and the next day 10.9 mg per cent. Twelve grams of calcium chloride were given daily by mouth until March 4, when a sharp decrease in the carbon dioxide combining power of the blood suggested a change to calcium lactate, 12 grams a day by mouth. A few days later, on March 9, the fifteenth postoperative

day, there occurred a manifest attack of tetany (blood calcium 7.9 mg per cent) that was treated satisfactorily by means of calcium gluconate intravenously. Following this episode the daily dose of calcium was increased to 20 grams of calcium lactate and 6 grams of calcium chloride. This was continued until April 1, after which 12 grams of calcium carbonate were taken daily for six months. Ten drops of viosterol were given daily until the summer months when sun baths were substituted.

During the postoperative period the anemia had recurred and this was treated by means of ferrous sulphate and liver extract.

On March 21, the basal metabolic rate was minus 27 per cent and a one grain thyroid tablet each day was prescribed.

The symptomatic improvement following the operation was slow and quite gradual but has continued throughout the eight months since the operation and has now reached a very satisfactory level. The patient walks and moves in general with a great deal more feeling of freedom. She rises from a chair without the assistance of her hands and she states that she feels better than she has felt for at least ten years.

The recalcification of the bones has been prompt and gratifying. Histological examinations in other cases have shown that immediately following the removal of the parathyroid adenoma the excessive activity of the osteoclasts ceases and the rebuilding of bone begins. This is, however, as a rule not appreciable in roentgen-ray films for several months. In this case the recalcification of the bones was slight but noticeable four weeks after the operation. Four months after the operation there was a marked improvement in the general calcium content of the bones as judged by the roentgen-ray films and almost complete filling of all the localized lesions by deposits of calcium. At this period the appearance of the roentgenograms suggests that larger amounts of calcium have been deposited in the sites where the lack of it was greatest. The calcium deposits are dense after four months in the two large lesions in the ribs, in the phalanges of the right fore-finger and in the round cyst-like area in the ischium.

Roentgen-ray films taken eight months after the operation show a further recalcification of the bones in general and there is now the appearance at the site of the former localized lesions of more nearly normal bone, somewhat less densely calcified than in the films taken four months after the operation.

The latest check of the blood chemistry in this case showed calcium 11.3 mg per cent and phosphorus 3.6 mg per cent. These figures may be accepted as normal although the figure of 11.3 for the calcium may appear a little high. It may be considered, however, in connection with the finding of the value of 7 gm per cent for the total plasma proteins, a figure higher than previously obtained in this case. On consulting the chart prepared by McLean and Hastings, it may be seen from their calculations that with a blood plasma protein of 7 gm per cent and calcium of 11.3 mg per cent the ionized calcium is approximately 5.05 mg per cent. It is supposedly the ionized calcium that is of importance in parathyroid disease.

COMMENT

Since Mandl's demonstration of change in metabolic abnormalities following the operative removal of a parathyroid adenoma in 1925, a fairly large number of cases has been reported. Wilder and Howell, in their recent review of the literature, state that they are willing to accept 135 definitely proved cases since the date of Mandl's publication. These authors point out the apparently very unequal distribution of this disease geographically with a relatively large number of patients being reported from the North Atlantic states, especially Boston.

The features of special interest in the case here reported include (1) The definite history of a disturbance in calcium metabolism with an inadequate supply of calcium and manifest tetany about 17 years before the operation. This fur-

nishes a possible or even quite probable basis for a stimulus to parathyroid over-activity and it seems probable that during this period the embryonic cell rests with parathyroid potentialities received the stimulus that resulted in the growth of an adenoma

(2) The variations from time to time in the intensity of the metabolic disturbance are obvious. These variations during our periods of observation within the space of a single year were such that at the first opportunity a diagnosis could not be made and 10 months later all signs were well marked. The disease, however, certainly goes much further back than the time of our initial examination for there is the history of fractures of the left fore-arm 18 months before we first saw the patient. While these fractures were not necessarily pathological fractures, yet in view of subsequent events it seems highly probable that they were. The general symptomatology, too, that is quite characteristic also in the light of after events certainly goes back for several years. Thyroid feeding may add materially to the decalcifying process in the bones but it seems unlikely that our prescription for thyroid changed the course in this case greatly for she had been receiving thyroid medication at intervals during the past several years. A possible partial explanation of the more rapid progress in the *ostitis fibrosa cystica* during 1935 may lie in the cessation of the calcium therapy which she had taken frequently during the preceding several years. It has been shown by Albright and others that feeding of calcium retards the decalcification of the bones in *ostitis fibrosa cystica* but perhaps renders the patient more liable to renal complications.

(3) The symptomatic recovery or improvement was much less dramatic than is often described. It was, on the other hand, slow and gradual but just as gratifying ultimately after a period of eight months.

(4) The recalcification of bone in this case seems definitely more rapid than that usually described. This may be due in part to the full doses of calcium taken by mouth over the period of seven months following the operation. Viosterol was taken during several of these months and sun baths during the summer. In regard to the recalcification of the localized lesions it is said usually that giant celled tumors recalcify satisfactorily and that cysts do not. There is no clinical criterion by which cysts can be certainly distinguished from tumors. In this case all localized lesions have recalcified with the exception of a portion of one lesion in the phalanx which is not yet filled after eight months. The roentgen-ray appearance of these local lesions after four months is certainly that of a relatively disorganized and heavy mass of calcium deposit surrounded by a very narrow rarefied line that enables one to recognize the lesions readily. In the films after eight months these lesions are less easily distinguished from the surrounding bone and the bony structure within them seems definitely more nearly normal.

REFERENCES

- 1 WILDER, R. M., and HOWELL, L. P. Etiology and diagnosis in hyperparathyroidism, Jr Am Med Assoc, 1936, cv1, 427-431
- 2 McLEAN, F. C., and HASTINGS, A. B. Clinical estimation and significance of calcium-ion concentrations in the blood, Am Jr Med Sci, 1935, clxxxix, 601-613
- 3 ALBRIGHT, F., AUB, J. C., and BAUER, W. Hyperparathyroidism, Jr Am Med Assoc, 1934, cxii, 1276-1287

PRIMARY CARCINOMA OF THE JEJUNUM, REPORT OF A CASE*

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PRIMARY carcinoma of the jejunum is of exceedingly rare occurrence. From the case reports of various European and American clinics, the incidence of primary carcinoma of the jejunum varies from 0.3 per cent to 1.0 per cent of all carcinomata involving the gastrointestinal tract from the cardiac end of the stomach to and including the rectum. Carter,¹ reviewing the literature up to 1935, found less than 100 cases reported of primary carcinoma of the jejunum discovered at operation, although a considerably larger number of necropsy cases had been reported. In the files of the Mayo Clinic prior to June 1936, Nettrour² found 31 proved cases of this entity, including both the operative and necropsy cases. As reported also by Rankin and Mayo,³ carcinoma of the large bowel, including the cecum and rectum, was found in this clinic 80 times as frequently as carcinoma of the small bowel. Of the cases of carcinoma of the small bowel, 38 per cent occurred in the jejunum. A surprising number of these were at, or a short distance from, the ligament of Treitz.

In a series of 41,883 autopsies at the Vienna General Hospital including 343 cases of intestinal carcinoma, Johnson⁴ was unable to find a single case of primary carcinoma of the jejunum.

Raiford⁵ in 1932 collected from the literature 339 benign and malignant tumors of the entire small intestinal tract, and reported 88 cases among 56,500 surgical and autopsy specimens from the Johns Hopkins Hospital, the malignant tumors included 3 surgical cases of primary jejunal carcinoma.

Further emphasis was laid on the rarity of this lesion in 1930 by Newton and Buckley,⁶ who in summarizing the reported statistics of European clinics and adding personal reports from eight of the largest hospitals in this country, listed only 35 histologically verified cases among 135,000 autopsies.

Since the opening of the Roosevelt Hospital in New York in 1871, according to Cave,⁷ only three specimens of carcinoma of the jejunum are entered in the laboratory files.

Pathology Primary carcinoma of the jejunum is practically always, histologically, of the adenomatous type. By far the most common in occurrence is the annular, constricting variety, the other rarer type being the polypoid, ulcerating and non-constricting lesion.

Metastases occur late. In Rankin and Mayo's³ series, serious metastatic involvement of the peritoneum and lymph nodes was found at operation in one-third of the cases. The mesenteric lymph nodes and peritoneum are usually first involved, then the liver, lungs, long bones and spinal dura in order. In the cases reviewed by Carter,¹ the mesenteric lymph nodes were enlarged in 75 per cent of the cases. In his opinion, further enlargement of the retroperitoneal nodes does not necessarily mean malignant extension nor do they preclude the advisability of radical resection, as the nodes may be inflammatory.

Symptoms From a review of the cases reported it would appear that the onset of symptoms is most insidious and the duration quite variable, being from

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two or three months to five years or more. The types of symptoms presented are in direct relation to the degree of intestinal obstruction produced and the existing anemia. With non-obstructing lesions the early symptoms are usually those of weakness, weight loss, and easy fatigability, due, presumably, to the gradual loss of blood and interference with the normal absorptive power of the small intestine. In all cases loss of weight has been a constant finding. Rankin reported an average loss of 28 pounds in his series.

A mild or moderate secondary anemia usually exists even in the earlier cases, the blood loss being occult in character and rarely are tarry stools reported. This, of course, is accounted for by the absence of an ulcerative stage in the development of the majority of the growths encountered.

Pain is not a symptom of frequent occurrence in the case reports of lesions found at or near the ligament of Treitz. Distention of the duodenum and first portion of the jejunum apparently occurs without producing the characteristic cramp-like pain complained of in obstruction resulting from intrinsic lesions of the ileum and colon. The character of the pain, however, varies with the degree of existing stenosis. It is usually localized in the region of the umbilicus, as is somewhat characteristic of other lesions of the small bowel, and may be sharp or dull and may seem to shift about somewhat in the abdomen, accompanied by borborygmus. Steady pain in the epigastrium is a late symptom and probably results from metastasis to the retroperitoneal lymph nodes. The onset of pain bears an inconstant relationship to the intake of food or alkalis.

In keeping with the insidious onset and long duration of symptoms in many instances, the attacks of pain are often followed by long periods of remission, the obstruction of the lumen apparently subsiding temporarily, leaving the patient free of discomfort during the interim. As the disease advances, however, exacerbations occur more frequently and sooner or later nearly all cases develop nausea and vomiting.

The time of onset of vomiting depends primarily upon two factors, the degree of existing obstruction and the proximity of the obstructing lesion to the pylorus. Carter,¹ in a review of 30 cases reported from 1927 to 1935, found vomiting to be a clinical feature in 28 cases. The vomiting may be profuse if the stenosis is high, and the vomiting of large amounts of grayish green fluid containing bile and particles of undigested food is typical of obstruction near the ligament of Treitz. This type of vomiting is observed in a large percentage of late cases and constitutes one of the most characteristic symptoms. The absence of fecal vomiting is also significant.

Varying degrees of constipation are reported, sometimes with alternating periods of diarrhea.

Physical Findings. In the early stages there is an absence of positive findings on physical examination. Later, an evident loss of weight and the pallor of the secondary anemia manifest themselves. Abdominal distention, in contradistinction to that seen in obstruction involving a more distal portion of the bowel, is usually very slight or absent. Visible and reverse peristalsis may be present. An abdominal mass is usually not palpable until after metastasis occurs.

Diagnosis. Clark,⁸ in 1926, found that an early diagnosis of carcinoma of the jejunum had not been made in any of the cases reported up to that time, due probably to the absence of tangible clinical symptoms and positive roentgen-ray findings. The roentgenologic diagnosis depends upon the presence of obstruction

and no case report was found in which even a roentgenologic diagnosis was made before obstruction occurred

Primary carcinoma of the jejunum occurs in persons relatively younger than those in whom carcinoma develops elsewhere in the intestinal tract. The decade of greatest incidence is the age period between 30 and 40, and men are affected twice as frequently as women.

The fact should be kept in mind that pain arising from lesions of the small bowel is more or less characteristically referred to the region of the umbilicus and that it usually bears some inconstant relationship to the taking of food.

All cases with beginning cachexia or gastrointestinal disturbances associated with the persistent and unaccountable finding of occult blood in the stools, merit a thorough roentgen-ray study of the entire small intestinal tract, with the thought in mind of a possible malignancy in this portion of the bowel. This consideration is of prime importance, particularly in those instances in which the bleeding is unaccounted for after a double-contrast barium enema study and sigmoidoscopy.

In the presence of the vomiting of large amounts of bile-stained fluid, as previously described, the diagnosis should always be suspected. Pyloric stenosis may be closely simulated.

In spite of suggestive symptoms and clinical signs, roentgenologic findings afford the only early positive preoperative diagnostic criteria. A preliminary flat plate of the abdomen may prove of value in demonstrating dilated loops of small bowel, thus indicating an obstructive lesion somewhere above the ileocecal valve. Under normal conditions, except in infancy or in cases where the ileocecal valve is incompetent, the roentgen-ray should not reveal gas in the small bowel.

The roentgen-ray diagnosis depends upon the presence of obstruction, which in itself precludes the advisability of administering barium by mouth except with caution. A serial study at hourly intervals with a small barium progress meal is, of course, the preferred technic when this lesion is suspected. Any delay in the emptying of the small intestine beyond 10 hours should arouse suspicion. In those few cases reported in which the diagnosis was made preoperatively, there was shown by roentgen-ray delayed emptying of the stomach, dilatation and atony of the proximal jejunum or duodenum, or stenotic peristalsis in the occluding type. Rarely has a frank defect in outline of the jejunum been demonstrated.

Treatment Radical resection with an end-to-end or side-to-side anastomosis is the surgical procedure of choice in these cases. Palliative side-tracking operations are indicated if this is inadvisable. Postoperative roentgen-ray therapy is justifiable.

Radical resection resulted in a mortality of 36 per cent in 70 cases of carcinoma of the jejunum or ileum reviewed by Hellstrom.⁹ The immediate mortality, however, was 70 per cent in those cases in which operation was performed during the stage of acute obstruction and only 18 per cent in those cases in which operation was done when no acute obstruction was present.

Prognosis The follow-up results in the cases in Hellstrom's series showed a definite cure in 16 per cent. However, no patient in Rankin and Mayo's series lived more than three years and the duration of life after the diagnosis was

established ranged from one month to three years, the average being less than a year

By means of improved roentgen-ray technic, the establishment of an early diagnosis in primary carcinoma of the jejunum, it is to be hoped, will make possible a larger number of radical resections with cure, since distant metastasis is apparently relatively uncommon

CASE REPORT

W B, white male, aged 35 years, salesman, married, was admitted to the Medical Ward of the Presbyterian Hospital on July 30, 1936. The patient was working regularly up to the time of admission. The presenting complaints were extreme weakness, loss of 10 pounds in weight in the past three months, tarry stools, and a very

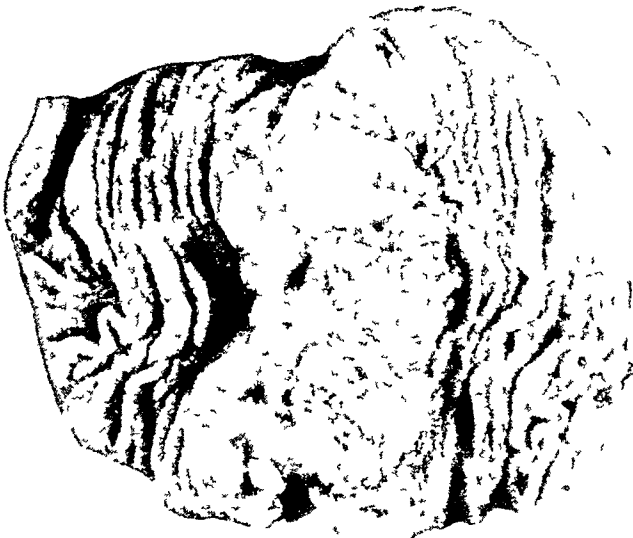


Fig. 1

FIG 1 Primary carcinoma of the jejunum, 20 centimeters distal to the ligament of Treitz

occasional pain, for the past nine months, just above the umbilicus, without relationship to food-intake, but relieved by alkalis. Appetite was good and there was no history of nausea. There had been vomiting on one occasion only, three days before admission, following the drinking of a large amount of wine. The past medical history was insignificant except for the existence of moderate constipation for the past two years.

The family history was interesting, in that the patient's mother died of some type of intra-abdominal cancer, and a sister died of cancer of the uterus.

Physical examination was essentially negative, except for marked pallor of the skin and mucous membranes, a systolic blood pressure ranging between 90 to 100 mm of mercury, and a very slight degree of tenderness on deep palpation midway between the ileocecal junction and the umbilicus. No mass was palpable in the abdomen. The liver and spleen were not palpable.

The Wassermann and Kahn tests were negative. Routine blood chemical tests gave normal results. The blood count on admission revealed a hemoglobin of 52 per cent, red blood cells 3,740,000. Fractional gastric analysis showed a grade I hyperchlorhydria, but no fasting retention and no blood. All stools were strongly positive for occult blood. Sigmoidoscopy failed to reveal any source of bleeding.

In view of the location of the pain, the relief obtained with alkalis, the hyperchlorhydria and the persistence of tarry stools, a tentative diagnosis of bleeding duodenal ulcer was made, roentgen-ray studies being postponed until diminution of the bleeding occurred.

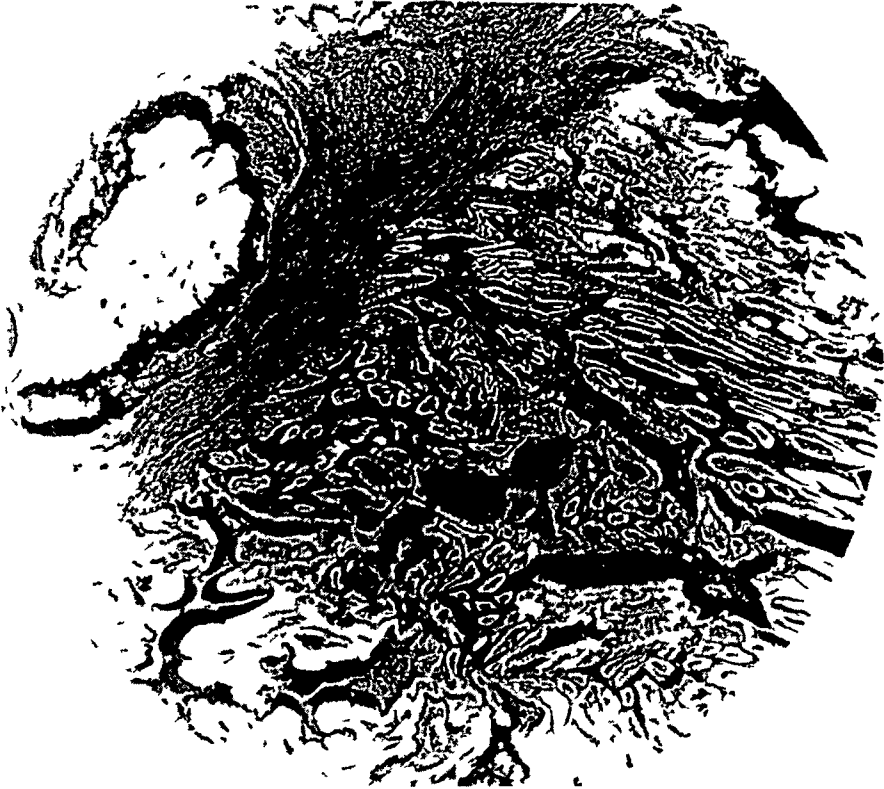


FIG 2 Section of the tumor mass, reduced from a photomicrograph with a magnification of 100 diameters

On a strict Sippy ulcer regime, with the administration of alkalis, the patient became symptom-free within a few days, and from then on had no subjective symptoms. He never complained of nausea, and there was no vomiting at any time, which was difficult to explain in view of subsequent findings. However, the red blood count and the hemoglobin continued to fall, reaching their lowest level at 2,730,000 red blood cells, with a hemoglobin of 49 per cent. A total of six blood transfusions was given, but the red blood count on 13 occasions during the preoperative period never became elevated above 4,300,000 cells per cubic millimeter.

The first gastrointestinal roentgen-ray study was made on September 1, 1936, and revealed an inability to fill out the duodenal cap. Fluoroscopically there was a constant deformity and irregularity of the cap on the films, but no typical ulcer niche was demonstrated. It was significant to note that there was an absence of any six

hour retention of barium in the stomach. A double-contrast barium enema study was negative.

In view of this apparently confirmatory roentgen-ray finding, treatment for a bleeding duodenal ulcer was continued. The stools, however, remained strongly positive for occult blood, and the secondary anemia persisted.

The second roentgen-ray study, on September 14, 1936, showed some improvement in the appearance of the duodenal cap, and there was still an absence of gastric retention at the end of six hours. No filling defect in the small intestinal tract was demonstrated beyond the duodenal cap.

At this point further medical treatment was deemed inadvisable, so, following a surgical consultation, laparotomy was performed by Dr. William Bates on September



Fig. 3. Section of the tumor mass, reduced from a photomicrograph with a magnification of 450 diameters.

18, 1936. A constricting annular carcinoma of the jejunum was found 20 centimeters distal to the ligament of Treitz (figure 1), the lumen through the lesion measuring 1 centimeter in diameter. Many of the regional mesenteric lymph nodes were found to be enlarged and there was one small nodule on the under-surface of the liver. The stomach and duodenum were normal, there being no evidence whatever of ulcer. The operation consisted of a resection of 11 centimeters of the jejunum with an end-to-end anastomosis. Several of the attached enlarged mesenteric lymph nodes were removed for biopsy.

The pathological report was as follows: Specimen consists of a section of the jejunum 11 centimeters in length with the attached mesentery and lymph nodes. In the middle portion of the section is a completely encircling growth which is 3 centi-

meters in width, obstructing the lumen so that it was only 1 centimeter in diameter through the lesion. The surface of the same has smooth and roughened areas. The cut surface has a pale pink color and is homogenous. In the attached mesentery there are several small, firm lymph nodes. *Microscopic* Sections through the intestinal wall and mass show normal mucosa ending abruptly at the mass which is composed almost entirely of large and small irregular shaped glandular structures supported by a small amount of fibrous tissue (figure 2). The lining epithelium is tall columnar but the cells vary in size and the nuclei have lost their polarity (figure 3). The nuclei vary in size, shape and density of staining. No mitoses seen. The supporting stroma is infiltrated by eosinophiles. The glands do not invade the muscularis. The lymph nodes do not show any evidence of metastasis. *Diagnosis* Primary adenocarcinoma of jejunum.

The patient made a very successful postoperative recovery, and was discharged from the hospital October 7, 1936, three weeks following operation. Since then improvement has been steady, he has been symptom-free, is gaining weight, and has returned to work. Deep roentgen-ray therapy has been given regularly since. A gastrointestinal roentgen-ray study, on December 10, 1936, showed a normal passage of barium through the jejunum. He was last seen on April 27, 1937, at that time he had gained 11 pounds since the operation, was symptom-free and having normal bowel movements with the use of mineral oil. Examination of the abdomen revealed no tenderness, no palpable induration and the liver was not palpable. Systolic blood pressure was 130 mm of mercury and diastolic 80 mm. Hemoglobin was 84 per cent and red blood cells 4,600,000. Stool specimens were negative for occult blood.

Note Since this case report was submitted, the patient has been seen on several occasions, the last examination having been made on June 13, 1938. At that time he showed a further increase in weight, was entirely symptom-free, and bowel function was normal. The blood count was also normal. Abdominal examination again revealed no palpable enlargement of the liver, and no intra-abdominal mass.

SUMMARY

- 1 Primary carcinoma of the jejunum is of interest because of its extreme rarity of occurrence.

- 2 The lesion is usually of the annular, constricting, adenomatous type.

- 3 The average duration of symptoms is about one to one and one-half years.

- 4 The earliest symptoms are systemic in character, namely, weakness, weight loss and fatigability, accounted for by the constant blood loss with a resulting secondary anemia.

- 5 The persistent presence of occult blood in the stools, otherwise unaccounted for, should lead to the suspicion of possible malignancy of the small bowel.

- 6 The more advanced symptoms and signs are in relationship to the degree of intestinal obstruction.

- 7 The vomiting of large amounts of grayish green fluid containing bile and food particles is suggestive of obstruction near the ligament of Treitz.

- 8 An abdominal mass is usually not palpable until after metastasis occurs.

- 9 Metastasis occurs late and distant metastases are relatively uncommon.

- 10 Radical resection with an end-to-end or side-to-side anastomosis is the surgical procedure of choice.

- 11 The prognosis is poor. The hope for improved prognosis lies in the earlier establishment of the diagnosis, by means of improved technic in the roentgen-ray study of the small intestinal tract.

- 12 A typical case diagnosed at operation is reported.

REFERENCES

- 1 CARTER, R F Carcinoma of the jejunum, report of three cases, Ann Surg, 1935, cii, 1019-1028
- 2 NETTROUR, W S Carcinoma of the jejunum, report of a case, Proc Staff Meet Mayo Clin, 1936, xi, 356-360
- 3 RANKIN, F W, and MAYO, C, 2ND Carcinoma of the small bowel, Surg, Gynec and Obst, 1930, 1, 939-947
- 4 JOHNSON, R Carcinoma of the jejunum and ileum, British Jr Surg, 1922, ix, 422
- 5 RAIFORD, T S Tumors of small intestine, Arch Surg, 1932, lxxv, 122
- 6 NEWTON, F C, and BUCKLEY, R C Primary adenocarcinoma of the jejunum, report of two cases, New Eng Jr Med, 1930, ccii, 255-261
- 7 CAVE, H W Carcinoma of the jejunum, report of three cases, Ann Surg, 1935, cii, 1097-1101
- 8 CLARK, E D Carcinoma of the small intestine, Surg, Gynec and Obst, 1926, xliii, 757-763
- 9 HELLSTROM, JOHN Primary cancer of the jejunum and ileum, Acta Chir Scandinav, 1927, lxi, 465

EDITORIAL

STATE PSYCHOPATHIC HOSPITALS

THE general medical profession has a definite interest in the construction by the State of new types of hospital facilities. Since there is an active movement on foot towards the construction of psychopathic hospitals in a number of states not yet possessing such units, a discussion of some of the problems involved may be of value.

A psychopathic hospital, as distinguished from a state or private hospital for the care of mental patients, or an insane asylum in the older terminology, may be defined as an institution to which patients presenting symptoms of mental disease are admitted for intensive diagnostic study or for a brief period of treatment, but not for permanent institutional care. Such institutions are also considered to have both research and educational functions.

The first question that arises in connection with the establishment of a State Psychopathic Hospital is whether this unit should serve as a receiving hospital for the other State Mental Hospitals. It is a disputed point. It is obvious that each new admission to any mental institution should be thoroughly surveyed both physically and mentally, to determine as accurately as possible the pathogenesis of the mental symptoms present and to furnish a basis for a program of therapy. It is also conceded that the organization and equipment of a psychopathic hospital are ideally fitted for this task. There are, however, definite disadvantages to be considered. In the first place the number of admissions to the State Mental Hospitals in the average state is very large. To pass all of these through the psychopathic hospital and still maintain a high standard of work in this institution would require a very large psychopathic hospital—which in view of the high maintenance cost of such institutions is not feasible in most states. Furthermore, by this plan the large mental hospitals of the state would receive all their patients with a sheaf of reports from the Psychopathic Hospital, if they repeated the work done they would be unnecessarily duplicating expensive procedures and if they did not they would be limiting themselves, to a considerable degree, to the task of custodial care. It is certainly vital that the work of physicians in the large mental hospital include experience in the diagnostic survey of new patients. Moreover, from the point of view of the State Psychopathic Hospital there would be a serious disadvantage in handling all the new cases of the state for inevitably the pressure of admissions would enforce a rapid turnover which in turn would tend towards routine types of study, towards decrease in the length of the period of observation and towards insufficient time for careful investigation of new diagnostic and therapeutic procedures. Finally the admission of all new cases to the State Psychopathic Hospital would entail moving many

of these cases very considerable distances from the far corners of the state only to have to return many of them for definitive treatment to the State Mental Hospital nearest to their homes

An admissions policy for the State Psychopathic Hospital which seems to combine service to the community, to the other State Mental Hospitals, and to its own educational and research functions may be somewhat arbitrarily outlined under the following heads

(1) The State Psychopathic Hospital should admit, as far as its capacity permits, all such unusually puzzling or complicated cases as are referred to it, because of its special diagnostic facilities and its consultant connections, from the admitting offices of State Mental Hospitals

(2) The State Psychopathic Hospital should admit directly cases from its own Out-Patient Department or referred to it by outside physicians for voluntary commitment if such cases are thought to require hospitalization

(3) Acute temporary mental conditions (deliria, etc.) arising in patients on medical and surgical wards of general hospitals may necessitate the removal of such cases for the sake of the other patients. In such instances the Psychopathic Hospital, if within reasonable distance, will offer a better combination of medical and psychiatric care than is usually available in a State Mental Hospital. It should be its policy to admit such emergency cases

(4) Patients whose own attitude, or that of their family, renders commitment to a State Mental Hospital difficult, may be cared for in the State Psychopathic Hospital under some modified form of voluntary commitment. Similarly many cases of psychoneurosis that do not need commitment may with profit to themselves be studied and treated in a Psychopathic Hospital

(5) Cases of mental disease applying for State care which fall into those groups which are being actively investigated in the State Psychopathic Hospital should be referred to this hospital for admission

There is very little question but what a Psychopathic Hospital should, if possible, be constructed in close physical connection with a large general hospital. The laboratory, roentgenologic, operating room and other facilities of the latter may thus cover the needs of the psychiatric unit. Moreover, the various specialties of medicine each with its diagnostic and therapeutic armamentarium will be represented in the general hospital and this material together with the specialist personnel will add greatly to the possibilities of a high standard of medical care for the patients of the Psychopathic Hospital

If there is a state-supported or state-owned medical school in the state then certainly it should be as the psychiatric unit of the general hospital of the state medical school that the State Psychopathic Hospital should function. The tremendous advantage is thus gained of utilizing this institution to educate the future physicians of the state in the principles of preventive and curative psychiatry. The integration of the psychiatric unit with the other

clinical departments of the hospital—the close relationship between the psychiatric out-patient clinic and the other out-patient clinics—the utilization of psychiatric consultants on the medical and surgical wards, and of medical and surgical or specialist consultants on the psychiatric wards—all these tend towards a more rational conception on the part of students and staff of the general hospital of the powers and the limitations of modern psychiatric methods—and towards closer reasoning and better acquaintance with disease among the psychiatrists

The educative functions of the Psychopathic Hospital are of course not confined to the students and staff of its affiliated general hospital. The time is certainly coming when hospital and out-patient experience with mental patients, especially in the earlier stages of their illness, will be a requisite for satisfactory training for internal medicine. Such graduate students of medicine will fill many of the interns positions in the psychopathic hospitals. The junior nurses also will come from the Training Schools which require psychiatric nursing experience. The psychiatric staff of such a state institution will naturally also take part in any campaign of lay instruction in mental hygiene.

In relation to research also there is an obvious advantage in close affiliation between the State Psychopathic Hospital and the State Medical School. The laboratories of the school, with their specialized personnel and equipment, would greatly influence and sustain the research endeavors of the psychiatrists. It should be the function of such a psychopathic hospital not only to do what it can to add to psychiatric knowledge, but especially to be the proving ground for the other State Mental Hospitals for new diagnostic technics and for new and promising methods of treatment.

When no medical school is available the State Psychopathic Hospital will possess somewhat less educational value and fewer research resources. It will strengthen itself by an alliance with any large public or voluntary general hospital, but should no doubt retain its autonomy as a part of the State Mental Hospital system. However, when it is closely integrated with the state medical school hospital it is probably best that it be considered an integral part of that hospital, administered by the director of that hospital, staffed by the Department of Psychiatry of that school, but working by definite agreements in full cooperation with the State Mental Hospital system.

REVIEWS

Tuberculosis of the Lymphatic System By RICHARD H MILLER, M D, F A C S, Assistant Professor of Surgery, Harvard Medical School, Associate Surgeon, Massachusetts General Hospital 248 pages, 22 × 15 cm The Macmillan Co, New York 1934 Price, \$4 00

In spite of the fact that tuberculosis of the lymph glands is growing steadily less common in this country, it still frequently presents a clinical problem to the practitioner. The author has worked for years in the Non-Pulmonary Tuberculosis Clinic of the Massachusetts General Hospital and the clinical aspects of the book are based upon this experience. There is an interesting historical account of scrofula and of the present incidence of glandular tuberculosis in different parts of the world. The author feels that the eradication of tuberculous cattle, the pasteurization of milk, the early extirpation of tonsils and adenoids and the more effective segregation of active human cases of tuberculosis have been the chief factors responsible for the decrease of glandular tuberculosis. He discusses the clinical features presented by tuberculosis in the different glandular groups in the body and their complications. The results with various modes of therapy, surgery, tuberculin heliotherapy, irradiation, etc., are analyzed and figures presented. Radical excision where feasible is favored. Of particular interest is the description of the routine employed in the investigation of the patient's family, home and occupation and the regulations advised in relation to contagiousness.

It is a valuable small monograph for all internists

M C P

The Lung By WILLIAM SNOW MILLER, M D, Sc D 209 pages, 10 × 16½ cm Charles C Thomas, Springfield, Ill 1937 Price, \$7 50

The medical profession owes to a group of Dr Miller's friends the opportunity of possessing in a single volume the gist of his many years of anatomical research on the structure of the lung. To internists who are interested in the rapidly advancing field of the mechanics of respiratory disease the basic facts concerning the construction of the bronchial tree and the alveoli, their blood and lymph supply, and their pleural covering will be of keen interest. As a reference book it will meet a wide demand. The illustrations in color of reconstructions of anatomical detail are very helpful, and the numerous other illustrations greatly increase the value of the book. The historical note on the work of those investigators who contributed most to our knowledge of lung structure is very illuminating. The volume should be in the library of all students of pulmonary disease.

M C P

Heart Disease in General Practice By PAUL D WHITE, A B, M D, Assistant Professor of Medicine, Harvard University Medical School, Edited by MORRIS FISHBEIN, M D 338 pages, 19 5 × 13 cm National Medical Book Co, Inc, New York 1937 Price, \$3 00

Dr White has written this small manual in the form of questions and answers. He has grouped these under the following main headings: Historical Introduction, Diagnosis, Prognosis, Treatment. There are numerous subdivisions under each heading. For instance under diagnosis there are sections on symptoms, signs, blood pressure, electrocardiography, etc. The questions are highly practical. Is there such a condition as acute dilatation of the heart? Is syncope due to heart disease

or heart weakness? What disorders of cardiac function are important and what unimportant?

Not every good teacher can employ the Socratic method to advantage Dr White can The book is worth reading and rereading It is small, light and inexpensive, moreover, and these qualities should extend its circulation

M C P

Why We Do It By EDWARD C MASON, M D 177 pages, 20 × 13.5 cm C V
Mosby Co, St Louis 1937 Price, \$1.50

The author has written a small book for the laity in which he discusses in a simple way some of the fundamental psychiatric conceptions as to the interests which affect human conduct, the development of personality, the sexual factor, social development, and the neuroses and psychoses The lay reader will find it not only interesting, but wholly intelligible and in many instances helpful It will be read with profit by medical students in their first year, and by older students of medicine who graduated without grace of psychiatric instruction

M C P

Step by Step in Sex Education By EDITH HALE SWIFT, M D 207 pages The
Macmillan Co, New York 1938 Price, \$2.00

This book should be very welcome to those of us who are called upon to advise parents as to how they should discuss sex with their children The author is a Visiting Lecturer at Wayne University and Director of the Family Consultation Service, Detroit It is obvious from the book that she has had considerable experience in advising about sex education

The unique feature about the book is that all the material is presented as imaginary dialogues or discussions The four characters used are a mother, father, son and daughter The parents started teaching the children from the age of two years and carry them up to twenty years No parent is expected to follow any part in detail, but parents who read the book through will learn principles which can guide their answers to their children's questions The most important topics are adequately covered The basic principle on which the book is written is one of frank, unembarrassed handling of any topic, with a minimum of moralizing In this respect the book measures up to the best standards of progressive education and mental hygiene

H W N

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library are gratefully acknowledged

- Dr Louis Faugeres Bishop, Jr, F A C P, New York N Y—2 reprints,
Dr Perk Lee Davis (Associate), Philadelphia, Pa—3 reprints,
Dr Leon S Gordon (Associate), Washington, D C—1 reprint,
Dr Herbert T Kelly, F A C P, Philadelphia, Pa—1 reprint,
Dr Lemuel C McGee F A C P, Elkins, W Va—11 reprints,
Dr Gordon B Wilder (Associate), Anderson, Ind—1 reprint
- Mrs Cary T Grayson, Washington, D C—Publication, "In Memoriam," containing reprints of articles appearing in the "Red Cross Courier" for March, April and May, 1938, on the life and works of the late Admiral Cary T Grayson (Associate)
- United Hospital Fund, New York, N Y—1 book, "Report of the Hospital Survey for New York," Volume III, 1938

DR MOHLER APPOINTED DEAN OF JEFFERSON MEDICAL COLLEGE

Dr Henry K Mohler, F A C P, Medical Director of the Jefferson Medical College Hospital of Philadelphia for the last twenty-four years, assumed new duties as Dean of the College on August 1, having been elected to this post by the board of trustees of the College on June 13

Dr Mohler was graduated from Jefferson Medical College in 1912 and the same year received his appointment to the resident staff of Jefferson Hospital. He became Medical Director of the Hospital in 1914, and was also named assistant physician to the Hospital

During 1913-14, he was in charge of the laboratory of clinical medicine in Jefferson Medical College and was elected instructor in medicine from 1913 to 1922. From 1922 to 1925 he was demonstrator in medicine, and in September, 1925, was elected associate in medicine, a post he held until 1929. He was elected assistant professor of medicine, November, 1929, associate professor of medicine in March, 1932, and clinical professor of therapeutics, June 30, 1936

Dr Mohler is also a graduate of the Philadelphia College of Pharmacy, and held the highest general average in his senior year and was awarded five prizes. When graduated from Jefferson Medical College, he held the highest general average in his senior year, was president of his senior class and was awarded five prizes

Dr Mohler is a member of many scientific medical societies, a past president of the Philadelphia Heart Association, a past president of the Pennsylvania Hospital Association, and has been a Fellow of the American College of Physicians since 1923

Dr E J G Beardsley, F A C P, Philadelphia, was the guest of the Northumberland County Medical Society June 9, 1938, and conducted a clinic at the Packer Hospital at Sunbury, Pa, and subsequently a round table discussion concerning the clinical material presented

Mercy Hospital, Chicago, has recently become University Hospital of Loyola University School of Medicine. It will be known henceforth as Mercy Hospital, Loyola University Clinics. Dr Robert S Berghoff, F A C P, Chicago, has been appointed Medical Director of the institution

Dr Louis F Bishop, Jr, F A C P, New York, N Y, addressed the Association for the Advancement of Industrial Medicine at New York City, May 18, 1938, on "Cardiovascular Syphilis"

Dr Bishop spoke on "Historical Landmarks of Cardiology" on May 2, 1938, before the Pre-Medical Society, the College of the City of New York

Dr Warren Coleman, F A C P, New York City, will retire from the practice of medicine in New York City and remove to Augusta, Ga, on October 1. It is probable that he will continue in consultation work and teaching at the University of Georgia School of Medicine

The Eleventh Annual Graduate Fortnight of the New York Academy of Medicine will be held October 24 to November 4, 1938, on "Diseases of Blood and Blood-Forming Organs". The program comprises afternoon clinics, evening meetings and scientific exhibits. Among those scheduled to present papers at the evening sessions are

- Dr George R Minot, F A C P, Boston "Etiology, Diagnosis and Treatment of Macrocytic Anemia" and "Other Forms of Hypochromic Anemia",
- Dr Cyrus C Sturgis, F A C P, Ann Arbor "Liver Therapy in Macrocytic Anemia",
- Dr Russell L Haden, F A C P, Cleveland "Diagnostic Significance of Changes in Erythrocytes",
- Dr Claude E Forkner, F A C P, New York "Common and Unusual Types of Leukemia"

Dr George M Decherd, Jr, F A C P, has terminated his appointment as Assistant Professor of Medicine at Louisiana State University Medical Center, New Orleans, to accept the appointment as Associate Professor of Medicine at the University of Texas School of Medicine at Galveston

At a meeting of the Brooklyn Society of Internal Medicine May 27, 1938, Dr Henry Monroe Moses, F A C P, was elected President and Dr Henry Dana Fearon, F A C P, was reelected Treasurer for 1938-39. Dr Moses succeeds Dr Frank Bethel Cross, F A C P

Dr Anthony Bassler, F A C P, New York City, was awarded the honorary degree of Doctor of Laws by Hahnemann Medical College of Philadelphia at its annual convocation in June. Dr Carl C Fischer, F A C P, Philadelphia, was awarded the honorary degree of Master of Arts

The Fourth Annual Symposium was presented by the Golden Clinic of the Davis Memorial Hospital, Elkins, W Va, June 25, 1938, with Dr R J Condry, F A C P, acting as chairman of arrangements. Dr Oscar B Biern, F A C P, Huntington, W Va, acted as a leader of a round table discussion at the West Virginia Heart Association Luncheon and Dr Lester Hollander, F A C P, Pittsburgh, gave a paper on "Dermatological Problems of the General Practitioner". Dr Lemuel C McGee, F A C P, is the internist to the Golden Clinic

Dr J Walter Torbett, Jr (Associate), formerly of Marlin, Texas, has accepted an appointment in the Department of Medicine at Louisiana State University Medical Center, New Orleans, as of July 1

Dr William G Herrman, F A C P , President of the Medical Society of the State of New Jersey, delivered one of the principal addresses in connection with the dedication of the new administration building and central unit of Bergen Pines, Bergen County Hospital, at Ridgewood, N J , on May 8

At the first annual meeting of the Iowa Pediatric Club, held in Des Moines, April 8, the guest speaker was Dr Julius H Hess, F A C P , Chicago, on "Chicago's Program for the Care of Premature Babies" Other speakers included Dr Walter L Bierring, F A C P , Des Moines, on "The National Program on Maternal and Child Health" and Dr Fred Sternagel (Associate), West Des Moines, who conducted a symposium on epidemic sore throat and scarlet fever

Dr Harold W Gregg, F A C P , Butte, Mont , was elected president-elect of the Medical Association of Montana at its last annual session during April

Dr Rufus Cole, F A C P , Director of the Hospital of the Rockefeller Institute, New York City, since 1909, was awarded the George M Kober Medal for distinguished service to medicine by the Association of American Physicians at its last annual meeting during May

Dr James Buren Sidbury, F A C P , Wilmington, N C , was installed as President of the Medical Society of the State of North Carolina at its annual meeting during May

Among those who presented papers on the program of the twenty-second annual scientific session of the Association for the Study of Internal Secretions at San Francisco, June 13-14, were Dr Daniel V Conwell, F A C P , and Dr Clarence J Kurth, Halstead, Kan , "Insulin Therapy in Mental Diseases", Dr Henry H Turner, F A C P , Oklahoma City, 'Infantilism with Congenital Webbed Neck and Cubitus Valgus", Dr Willard O Thompson, F A C P , Dr Phebe K Thompson, Dr Samuel G Taylor, III (Associate) and Dr William S Hoffman (Associate), Chicago, "The Treatment of Addison's Disease with Adrenal Cortex Extract"

Dr Wilham J Kerr, F A C P , San Francisco, delivered the presidential address on "Radiculitis Associated with Spinal Arthritis" before the annual meeting of the American Rheumatism Association at San Francisco, June 13 Other speakers included Dr Mark P Schultz, F A C P , Washington, D C , "Metabolic Factors in the Induction of Nonpurulent Carditis", and Dr Walter Bauer, F A C P , Boston, "Treatment of Gonorrheal and Rheumatoid Arthritis with Sulfanilamide"

Dr Jay A Myers, F A C P , Minneapolis, delivered the presidential address before the meeting of the American Academy of Tuberculosis Physicians at San Francisco, June 17-18 Other speakers on the program included Dr Charles W Mills, F A C P , Tucson, Ariz , "A Case of Fungus Coccidioides Infection Primarily in the Lung with Cavity Formation and Healing", Dr John M Nicklas (Associate), Valhalla, N Y , "The Tuberculous Child", and Dr Maxim Pollak, F A C P , Peoria, Ill , "Results of Effective Tuberculosis Control"

Dr James S McLester, F A C P , participated in a symposium on oxygen therapy before the Jefferson County (Ala) Medical Society, May 16, his subject being, "Clinical Response to Oxygen Therapy"

Dr Thomas Parran, F A C P, Surgeon General of the U S Public Health Service, was awarded the Mendel Medal for 1938 by Villanova (Pa) College recently in recognition of his scientific approach to the problems of public health

Dr William J Mallory, F A C P, Washington, D C, was inducted May 11 as President of the Medical Society of the District of Columbia Dr Coursen B Conklin, F A C P, was reelected secretary

Dr M C Pincoffs, F A C P, Professor of Medicine, University of Maryland School of Medicine, Baltimore, and Dr Beverley R Tucker, F A C P, Professor of Neuropsychiatry, Medical College of Virginia, Richmond, were among the instructors participating in the sixth annual graduate short course for physicians held at Daytona Beach, Fla, June 27 to July 2, under the auspices of the Florida Medical Association and the Florida State Board of Health

Dr Victor F Cullen, F A C P, State Sanatorium, Md, has been made a vice president of the Medical and Chirurgical Faculty of Maryland

Dr Edward L Turner, F A C P, Nashville, Tenn, has been appointed President of Meharry Medical College, July 1, to succeed Dr John J Mullowney, who has retired

Dr Anita M Muhl, F A C P, San Diego, addressed the twenty-third annual convention of the American Medical Women's Association at San Francisco June 12-14, on "The Doctor's Mental Attitude"

Dr Walter L Treadway, F A C P, Assistant Surgeon General of the U S Public Health Service, Washington, D C, has been appointed medical officer in charge of the federal narcotic farm at Lexington, Ky

Dr Raymond J Reitzel, F A C P, and Dr Stacy R Mettier, F A C P, have been promoted to Associate Clinical Professor of Medicine and Associate Professor of Medicine, respectively, in the University of California Medical School, San Francisco

The Medical Association of Georgia has announced that the L G Hardman Loving Cup honor for the past year will go to Dr Virgil P W Sydenstricker, F A C P, Professor of Medicine, University of Georgia School of Medicine This honor is awarded annually to the physician who is deemed to have rendered the most distinguished medical service during the previous year

Dr Reginald Fitz, F A C P, Wade Professor of Medicine at Boston University School of Medicine, conducted a round table discussion and presented a paper on "The Case of the Forsaken Pamphlet" at the first anniversary celebration of the Gerrish Memorial Library, Lewiston, Maine, on May 26

Dr George C Stucky, F A C P, for many years Superintendent of the Ingham County Tuberculosis Sanatorium, Lansing, Mich, has resigned to work on a rural health project being conducted in seven counties of Michigan by the W K Kellogg Foundation

On May 23 the Minnesota Public Health Association sponsored a testimonial dinner in honor of Dr F E Harrington, F A C P, Minneapolis, on the anniversary of the opening of the Lymanhurst Health Center, which he established seventeen years ago. Dr Harrington was sent to Minneapolis in 1920 by the U S Public Health Service. He urged the early establishment of a school for tubercular children, and in 1921 Lymanhurst was built.

The Board of Regents of the University of Oklahoma recently announced the following appointments on the Faculty of Medicine:

Dr Hull Wesley Butler, F A C P, Associate in Medicine and Associate in Histology,
Dr Minard F Jacobs (Associate), Instructor in Medicine,
Dr Bert Fletcher Keltz, F A C P, Associate in Medicine and Supervisor of Clinical Clerkships,
Dr Elmer R Musick (Associate), Associate in Medicine,
Dr Frederick Redding Hood (Associate), Associate in Medicine,
Dr William Ward Rucks, Jr (Associate), Associate in Medicine,
Dr Wilbur Floyd Keller (Associate), Associate in Medicine.

Dr Henry Kirvin Speed, F A C P, is President (1938-39) of the Oklahoma State Medical Association.

Major General Charles R Reynolds, F A C P, Surgeon General of the U S Army, Washington, has been designated by President Roosevelt to act as president of the permanent committee of the International Congress on Military Medicine and Pharmacy, to be held in Washington during May, 1939.

Dr F M Acree, F A C P, Greenville, Miss, is the Secretary-Treasurer of the Delta Medical Society.

Dr Felix J Underwood, F A C P, Jackson, Miss, has been elected President of the State and Provisional Health Authorities of North America.

Dr Henry A Christian, F A C P, Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, was the chief speaker on the centennial program of the Medical College of Virginia at Richmond on June 7.

Dr Robert S Palmer, F A C P, Boston, addressed the University of Virginia Medical Society recently on "Rationale and Results of the Surgical Treatment of Essential Hypertension."

Dr Walter B Martin, F A C P, Norfolk, is the chairman of the medical section of the Virginia Academy of Science.

Dr Rock Sleyster, F A C P, Wauwatosa, Wis, was made President-Elect of the American Medical Association at its San Francisco meeting in June. Dr Sleyster had previously served as Secretary, President and Treasurer of the Wisconsin State Medical Society, as Editor of the Wisconsin Medical Journal, as delegate to the House of Delegates of the American Medical Association for the Wisconsin State Medical Society and as a member (for two years chairman) of the Board of Trustees of the American Medical Association.

Dr James E Paullin, F A C P , Atlanta, Ga , was reelected to the Council on Scientific Assembly until 1943

Dr Nathan B Van Etten, F A C P , New York, N Y , was succeeded as the speaker of the House of Delegates by Dr Harrison H Shoulders of Nashville, Tenn

Dr Edward Weiss (Fellow) was a member of the group representing the Temple University Medical School which was awarded the Gold Medal for the exhibit on Cardiovascular-Renal Diseases at the recent meeting of the American Medical Association

Dr M Hill Metz (Associate) presented a paper, "Peptic Ulcer Treated by Posterior Pituitary Extract—Two Years Experience," at the annual session of the Texas State Medical Association, Galveston, on May 10, 1938

OBITUARY

DR GEORGE CAPLICE MILLER

Dr George Caplice Miller, of Seattle, died April 2, 1938, of acute leukemia, following an illness of less than one month

Dr Miller, the son of a physician, was born in St Marys, Kansas, December 17, 1886 He was graduated from St Louis University Medical School in 1909 and after his internship he was associated in practice with Dr William Engelbach for some time In 1917, he entered the army and served for the duration of the war

In 1919 he located in Seattle and for a few years was associated with a clinic, after which he practiced independently until his death

Dr Miller had an unusually busy practice but he found time for a great deal of charity work, particularly in connection with Catholic organizations and with the Providence Hospital He had been chief of staff of the Providence Hospital and his counsel was an important factor in the improvement of standards in that institution

Ever since the opening of the new King County Hospital in 1931, he had been chief of the medical division, a task to which he gave much time and thought

He is survived by his widow Mrs Helen Miller, two daughters and two sons

An unusually capable physician, a fine gentleman, he was widely known and he will long be remembered by the profession and the laity His death was the occasion of an editorial in a local paper, an indication of the important place he held in this community

C E WATTS, M D ,
Governor for Washington

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A CONSIDERATION OF THE ACQUIRED RESISTANCE OF FIXED TISSUE CELLS TO INJURY

By WM DEB MACNIDER, M D , F A C P , *Chapel Hill, North Carolina*

ONE of the many pleasant experiences that come to a person who has lived for years a laboratory type of life, one interested in investigation and especially if such study has had a certain continuity of purpose, is that an opportunity presents itself to review this work, to see it in a measure as a whole and as Bacon suggested, to catch the resemblances of things, one to another, which he considered was the main point in acquiring information which partook of understanding. Through an analysis of such resemblances one may be able with a caution to come to a composite type of conclusion in which experiments differing much in their initial purpose or even in their major objective tend to focus to a common point and shed light not only on a meticulous part of a problem but on such related problems that a principle may evolve based on reason dependent upon experimentation.

For nearly 30 years experiments have been in progress in this laboratory which have been primarily concerned with both the type of tissue reaction and the functional expression of such a reaction which develops in two organs, the kidney and the liver, when these organs are subjected to injury by certain mechanical manipulations or the action of a variety of chemical poisons. When chemical bodies were employed, they were selected in the hope of either injuring such organs in a diffuse manner or localizing their injurious influence to some particular part or structure in the organ. Injury to tissue associated with the survival of the organism participating in the injury, connotes the development of some type of repair process which enables the animal to make or to fail to make an organ adjustment both within the injured organ and also with such a repaired organ related to other structures in order that through such an adjusted state the animal may again participate in the life process. The order of this life process in terms of both function and resistance to subsequent injury depends upon

* An address delivered at the Twenty-second Annual Session of The American College of Physicians, New York City, April 7, 1938.
From the laboratory of pharmacology, The University of North Carolina

the type of cell effecting the repair. A repair by a baser, supporting tissue for highly specialized cells with a specific type of function results in an acquired resistance with an absence of functional adaptation. A repair by an altered type of cell resembling the cells which have degenerated may restore function to a certain level of pathological effectiveness and at the same time impart to such a repair process a degree of resistance to secondary injuries. Tissue repair when considered as a tissue adjustment with function is effected by tissue changes which fall into two categories of cytological reactions: cell recuperation or cell regeneration. In the former process of cell recuperation, cytoplasmic and nuclear readjustments occur which bring the injured tissue back to its cytological normal. It becomes of normal, functional value and shows the usual degree of susceptibility to injury. In the higher animals very little is known concerning this type of repair process. The give and take of highly specialized cells in the normal and, especially, in the pathological life process, injury, recuperation, with a transitory adjustment to an organ and organism environment are states which deserve extensive study and which will not be understood by waiting for the autopsy table to reveal a terminal event, death. Death dependent upon progressive changes of degeneration must be preceded during the life span by both chemical and morphological changes in cells, indicative of their elasticity, which make cellular adaptations possible. In addition to tissue reactions characterized by cellular recuperation, there is a second type of cell change, regeneration, which may develop as a repair process when a sufficient degree of injury has been inflicted that results in the formation of a normal type of cell of the usual functional value, or the cytological injury may be of such an order that a normal type of cell can not be formed. The severity of the tissue injury and the age of the animal in which such an injury takes place influence the type of functional cell which is formed. There may appear through a process of regeneration an abnormal, atypical form of cell with modified function and such cells may have acquired a resistance not only to the cause of the injury but to other agents of a harmful nature. A cell metaplasia has developed as a response to an injury which enables an organ to function and function perhaps at a lower level of effectiveness, yet, associated with the change in cell type, a resistance to injury has developed. It is this latter type of cell repair, a repair not of recuperation but one characterized by the formation of new cells, with which this discussion will be concerned. Here again it would appear worth while to emphasize the fact that cellular repair as regeneration may not take place by the formation of a normal type of cell. Such cells of repair under certain conditions appear to be unable to reappear as a normal order of cell for a given tissue location but, as a result of tissue reactions dependent upon injury, the ultimate nature of which is unknown, offer as a substitute cells of a changed type, certainly differing morphologically and presumably chemically from the normal cell. The development of such changes in cell form following a tissue injury may only constitute a transitory departure from the normal. In some instances

there appears to be an inherent tendency on the part of such atypical cells of repair to revert to a cell of normal configuration for a given tissue location. Such shifts in cell type have a place in any fundamental understanding of disease states. Their appearance upsets our conception of tissue repair invariably developing true to cell form for a given organ location and forces us to consider not only the cause, severity of injury, and age of the animal in which such cell reactions occur but in addition, the changed environmental state due to injury in which such a repair process has been able to develop and in which it must relate itself and persist. A repair process characterized by modification in cell form with function and with an acquired resistance may not be disease with an end reaction of death but life of a modified order with a transitory period of acquired protection.

Many years ago certain studies^{1, 2, 3} were undertaken to ascertain the type and extent of the injury which developed in the kidney of the cat when one branch of the renal artery was occluded by ligature. These studies were furthermore instituted in order to observe the processes of repair which might appear in such large areas of renal injury in which an adequate vascularization of the injured tissue had developed. Ligature of one of the main branches of the renal artery in the cat leads to the development of a large area of necrosis, the size of which depends upon which branch of the artery has been occluded. The central portion of such an area becomes completely necrotic and later undergoes a shrinkage. Connective tissue cells invade the greater portion of such areas while at their margins there occurs an ingrowth of blood vessels which is followed by a modified type of repair process. In many areas in such zones of injury the ingrowth of vessels is sufficient to permit an atypical type of epithelial repair process to develop in the region of the convoluted segment of the tubule. Such a process of epithelial repair in these areas of injury does not take place by the formation of normal cuboidal cells specialized in their internal structure but by the formation of a very flattened type of epithelium which either shows imperfect cell differentiation or occurs as undifferentiated syncytial structures. Nothing is known concerning the function, if any, of tubules lined by this type of epithelium. The relined tubules appear to end blindly and have between them a capillary network which is adequate as a source of nutrition to maintain the physical integrity of such an atypical epithelium. It would appear that in such zones of injury an altered organ environment has been established by restricting its blood supply to which a normal type of specialized epithelial cell is unable to effect its adjustment but that with a blood supply adequate to maintain in some measure epithelial life a process of epithelial repair is accomplished of a modified order, which epithelium is resistant and can adjust itself to the altered renal environment in which it makes its appearance. An epithelial adjustment has been made to an altered environmental status of an organ. Such a conception carries with it the assumption that the altered type of epithelium is of a resistant form and

that such an acquired resistance enables such cells to persist in areas which are unfavorable for the life of a normal type of cell.

A similar type of cell adjustment likely occurs in various organs which have been subjected to a sufficient degree of injury. It would appear to be especially common in the convoluted segment of the tubule in both epithelial and vascular types of nephritis, especially the latter. In such a form of renal injury, progressive arterial and glomerular damage leads ultimately to such a change in the blood supply of the kidney that a normal type of epithelial cell is unable to persist in this segment of the tubule. In its place are found atypical, flattened cells, frequently in syncytial configuration which are usually spoken of as cells of atrophy, flattened by pressure from within the tubule. Such a conception may or may not be correct. However, from an experimental point of view the more natural inference would be that such flattened cells represent an atypical type of epithelial repair which has been made necessary on account of a normal type of cell being unable to adjust itself to, live and function in, a renal environment so extensively modified by changes in its blood supply. Changes in epithelial type of a similar nature have been observed in the kidney of senile individuals and have been attributed by Kaufman⁴ to the aging process. Epithelial repair processes of the order under discussion may be a part of a mechanism which not only tends through the resistance of such cells to transiently stabilize a chronic nephritic with a certain degree of renal function but for a period to afford some degree of acquired renal resistance to injury. Such an interpretation of changes in cellular morphology enables one to see such changes not solely in terms of degeneration, but as shifts in cell type in given organ locations in order to effect an adaptation to a changed organ environment occurring either as a result of disease or as a part of physiological senescence. Cellular changes of such an order may result in lessened function, life at a lower level of effectiveness and yet afford a certain degree of protection to injury for periods variable in their duration. With such a conception of the significance of cell changes during the life span of an organism and developing as a process of repair secondary to injury, it becomes rather difficult to decide just what cellular events should be embraced by the term disease.

As a result of the interest developing from these early and simple experiments on tissue repair which have been referred to, work of a different experimental nature has been in progress in this laboratory for some years in which various chemical substances, especially the salts of uranium, have been used to effect an injury to either the kidney or the liver. During the period of such acute injuries and later when processes of repair were in progress, these organs have been studied histologically by the removal of biopsy material and by various tests which would give some indication of the functional value of such organs during the acute injury and at various stages of the process of repair. In addition to such observations, especially when uranium was used as the nephrotoxic or hepatotoxic agent, the animals have

been reintoxicated and subjected to both histological and functional studies in order to ascertain not only the state of function of such organs but to determine whether or not a state of increased susceptibility or one of acquired resistance had developed in the liver or the kidney as a result of the type of repair process which had been instituted from the initial acute injury^{5,6}

The fact has been known since the early work of Chittenden and Hutchinson⁷ that uranium salts have an affinity for the epithelial tissue of both the liver and the kidney. Suzuki⁸ was inclined to specifically localize this injury to a particular segment of the convoluted tubule. The injury is selective in this location in that it develops here as the earliest manifestation of the intoxication, but other tissues of the kidney, the glomeruli, are also injured as is shown not so much by acute changes but by the process of repair in these structures which finally advance to such a state of chronic degenerative injury as to constitute a chronic, vascular type of nephritis.

The ease with which both the acute and chronic changes can be induced in the kidney by uranium is in a measure determined by the age of the animal. Young animals show an epithelial resistance to this substance. The epithelial repair process in such an age group is usually characterized by the formation of a normal type of epithelial cell. Fibrosis and hyalinization of the glomeruli occur less readily in young animals than in adult animals. In contrast to the reaction of puppies and young animals to uranium, adult animals and certain senile animals show an increased susceptibility to both the epithelial and glomerular damage which may be inflicted by this poison. This variable, the factor of age, has to be taken into consideration not only in studying the severity of the acute injury but also in gaining information concerning the type of repair process which develops, especially in the epithelium^{9,10}. An understanding of the way in which the age factor influences epithelial susceptibility to injury and the type of epithelial cell repair, as well as the changes in the glomeruli, is difficult to ascertain, for there is but little accurate knowledge of what actually constitutes aging on the part of tissues. The severity of the epithelial injury certainly reflects itself in the type of repair process which is instituted by such tissue. This factor fails to operate in terms of the changes of repair induced in the glomeruli. Histologically, acute glomerular injuries of the same order of severity are followed by processes of repair which are essentially different in terms of the degree and completeness of chronic, glomerular degeneration. In puppies and young animals the glomerular injury is followed by an order of change which should be looked upon as a change of recuperation. In general the glomeruli return, following an acute injury to structures which are histologically normal. When these bodies are injured in adult and especially in senile animals, there occurs as a reaction of repair the formation of both capsular and intercapillary connective tissue which later undergoes hyalinization leaving the glomeruli for a period canalized, rather than capillary structures. From these observations it

would appear that the age of an organism such as the dog very largely determines the period in the life span of the animal at which connective tissue formation most readily develops in the glomeruli

In the following account of those changes of both injury and repair which develop in the kidney and the liver during the course of intoxications by uranium nitrate, the factor of age, on account of its significant influence, will be given adequate consideration

When young dogs are intoxicated by 2 to 4 mg of uranium nitrate per kilogram of body weight, the first evidence of renal injury which can be histologically demonstrated occurs in the convoluted tubule cells. Such cells show a deposition of stainable lipid material, cloudy swelling with edema and partial necrosis. The degree of necrosis is variable. No attempt will be made to interpret the functional expression of such an injury for in the higher animals tubular function, whatever it consists in, can only be separated from glomerular activity by inference. The repair process which develops in this location of the renal tubule in young animals from such a degree of injury is characterized by the formation of a normal, cuboidal type of cell, specialized in its internal structure, which, functioning in association with glomeruli that appear uninjured, restores the kidney to its normal functional value. With the completion of such a process of repair if these animals be given a second subcutaneous injection of the same amount of uranium nitrate per kilogram, the specialized cells which have effected the epithelial repair fail to show any evidence of an acquired resistance. An acute epithelial injury develops which may be of a severer order than the initial injury. A greater degree of necrosis occurs and lipid material in an increased amount appears in such damaged cells. Such secondarily intoxicated animals frequently fail to survive. Their death is of a renal type associated with the development of a marked disturbance in the acid-base equilibrium of the blood which at its commencement is out of proportion to the degree of renal injury as indicated by the various tests employed to ascertain renal function. These experiments indicate that when young animals are intoxicated by uranium nitrate an injury to convoluted tubule cells is induced which is not of a severe type. The repair process results in the formation of an epithelial cell of normal configuration which manifests no acquired resistance to secondary uranium intoxications. In certain of the animals these cells of repair are more susceptible to uranium injury than are the normal cells in this segment of the tubule.

The influence of the age factor in determining cell susceptibility and to an extent the type of cell repair is not only of general biological interest but assumes significance of a biological nature as applied to medical problems. Observations which are to follow indicate that in older animals the usual type of cell repair to convoluted tubule epithelium is by the formation of not only an atypical cell for this segment of the tubule but one which also is resistant to injury. Such modifications in cell structure as a reaction to injury may be a factor in deferring organ and organism senescence ^{11, 12}

The same factor may be operative to an extent in determining the type of disease process likely to develop at various age periods

The reaction of renal tissue of older animals to an intoxication by uranium nitrate is not only more severe but of a more diffuse nature than is the case with younger animals. The earliest evidence of injury in these animals is also expressed by processes of degeneration in the epithelium of the convoluted tubules. The epithelial injury is not confined to these cells but shows itself in the loops of Henle, especially the ascending limb, by a marked deposition of stainable lipid material. Furthermore, in animals of such an age group, regardless of whether the glomeruli show more evidence of acute injury than occurs in the younger animals, there develops an early and progressive connective tissue reaction in these structures, finally leading to their partial or complete obliteration as capillary bodies. In animals of such an adult or older age period the injury to the convoluted tubule cells is associated with the formation of lipid material as droplets or fused masses, edema and cell vacuolation terminating in a state of necrosis which is variable in its degree of completeness. Not infrequently in such cells the seat of severe damage, the nuclei stain well and appear in a fair state of preservation. A considerable number of animals showing such a degree of renal injury fail to survive the intoxication. Those effecting a survival institute a repair process to the damaged epithelial tissue which results in the formation of an entirely different order of cell for this segment of the nephron. Such cells are invariably flattened which in turn increases the diameter of the tubule. This increase in size of the tubular lumen is not due to the compression of a normal type of cell. It is due to a change in the morphology of the cells which line the convoluted segment and which make their appearance as a process of repair. Such a statement can only be made by a study of biopsy material during the period of repair. Understanding of such cellular events can never be obtained solely by autopsy observation. Death and the dead house eliminate the sequence of events as pathological life which finally expresses itself at the autopsy table. In addition to the flatness of these newly-formed cells of an atypical order which appear in the convoluted tubules as a reaction to a severe injury in an animal of an appropriate age period, the cells usually possess large, deeply staining nuclei and show imperfect cell differentiation. In other areas this segment of the nephron becomes lined by undifferentiated epithelial tissue in definite syncytial formation. In these structures the nuclei are irregularly placed. The origin of these atypical cells of repair is two-fold. In convoluted tubule segments the epithelium of which shows complete necrosis an attempt at repair, which has never been observed to be completed, may arise as a result of an ingrowth of cells from the descending limb of Henle's loop into the necrotic material which may remain in the convoluted segment. The usual mode of repair which reaches a state of completion is from the cells of the convoluted segment which have not participated in such a degree of injury as to make nuclear division and cytoplasm formation impossible.

Such a repair process does not take place uniformly throughout the damaged tubular segment but occurs in isolated areas. From such nests of regenerating epithelium the tubule becomes relined by a continuous epithelial layer either as a syncytium or as imperfectly differentiated, flattened, cell masses. A repair with an epithelium of an embryonic type has developed in animals of this age period following a sufficient degree of epithelial injury. It would appear that the degree of injury inflicted to such specialized cells is of great importance. A slight injury is insufficient to so change the constitution of cells as to prevent them from instituting a normal type of cell repair. With a severe injury to the same type of cell, especially if the injury takes place in an adult or senescent animal, an atypical form of cell appears as a repair process which has certain of the characteristics of embryonic tissue. Such an atypical type of cell repair affords protection to this formerly susceptible segment of the tubule as is shown by the fact that such cells are resistant to uranium nitrate intoxications when this nephrotoxic agent is used in an amount in excess of that necessary to induce a severe necrosis of normal cells¹³. An observation of a similar nature has been made when animals which have shown an acquired epithelial resistance to uranium are intoxicated by bichloride of mercury. This poison selectively injures in a normal animal the epithelium of the convoluted tubules. If the epithelium in this location of the tubule has changed its type as a result of a process of repair to an acute uranium injury, it has been found to have also acquired a resistance to bichloride of mercury. During such periods of epithelial resistance to both uranium nitrate and bichloride of mercury these nephrotoxic substances can be demonstrated in the urine¹⁴.

The experiments with uranium nitrate which have been briefly outlined indicate that a slight injury to the convoluted tubule cells from this substance is followed by a repair process which results in the formation of a normal type of cell both in its general morphology and in its internal structure. Cells of this order have failed to manifest any resistance to secondary intoxications by uranium. In other animals, especially those falling in an adult or senescent group, the use of this poison induces a severer type of tubular injury which is followed by a process of epithelial repair in which the cells are of an atypical type without specialization in their internal structure and which have certain characteristics of embryonic tissue. A repair of specialized, damaged epithelium by this order of cell imparts to the segment of the nephron in which it develops not only an acquired resistance to the nephrotoxic agent which induced the acute injury but to an injurious agent, bichloride of mercury, which specifically acts on that part of the tubule which has participated in the atypical type of epithelial repair. These experiments not only demonstrate an acquired resistance of the epithelial cells of repair to uranium and bichloride but in addition the observation is made that such cells are able to adapt themselves to those chronic changes of a vascular nature which develop in the kidney as a delayed but essential part of the uranium injury and which, when taken in conjunction with the

epithelial changes, constitute a chronic nephritis. The atypical cells of epithelial repair manifest three forms of resistance: a resistance to the substance which provoked their formation, a resistance to another type of certainly acting chemical poison, bichloride of mercury, and finally to a severely altered renal environment established by changes of degeneration in the glomeruli.

In experiments on the kidney in which the higher animals are used, it is impossible to evaluate except by inference, which may be very misleading, the degree of function which should be ascribed to such intimately inter-related structures as the glomeruli and the renal tubule. Even when nephrotoxic substances are used which have a selective affinity for renal epithelium it becomes impossible to ascribe departures in renal function to such an injury. Furthermore, when different types of epithelial repair processes develop in such tissue which may or may not have acquired a resistance to injury, it also becomes impossible to know whether or not such types of epithelium are of functional value. Such information is necessary in order to evaluate the significance of an epithelial repair. If such an epithelium is of no functional value, this type of repair which imparts resistance is useless to the organ in which it occurs and therefore to the organism as a whole. On the other hand, if the resistant type of epithelium, even though changed in its configuration and internal structure, possesses function of a normal type, then a tissue reaction has developed through a process of repair which enables organ survival as a functional entity and through such organ resistance a contribution is made to the survival of the individual.

In order to ascertain whether or not an organ, in which an atypical type of epithelial repair had developed which imparted resistance, was associated with function of a normal order, the liver has been chosen for investigation on account of the lack of dependency in this organ of the function of its epithelium on any other structure. In these experiments hepatic function has been estimated by determining the initial plasma concentration of phenoltetrachlorophthalein and the rate with which the dye is removed from the plasma by the normal liver, the liver the seat of an acute injury from uranium nitrate, and at periods of repair when such processes had been effected by the formation of both normal and atypical types of epithelial cells. This test gives little information in terms of relative quantitative values. It indicates the development of gross injuries to liver epithelium and in addition its use is of sufficient value to determine whether or not an atypical type of epithelial repair is of functional value and to a less extent the degree of function possessed by such a repair process.

In the experiments which are to be reviewed, the same observation has been made in connection with the susceptibility of the normal liver to injury as has been made for the kidney. In general, regardless of the weight of the animal and therefore the total amount of uranium received, this substance induces less evidence of epithelial injury to the livers of young

animals than it does to those of adult animals and the usual senile animal in which no change in this tissue has developed as a part of the senile state

An intoxication by uranium nitrate in the amount of 2 to 4 mg per kilogram of body weight is followed by an injury to the liver which consists in fatty infiltration of the epithelium, edema and cell vacuolation with scattered areas of necrosis. A diffuse liver injury of such an order is usually indicated by a slight increase in the initial plasma concentration of phenoltetrachlorophthalein and by some delay in its removal from the plasma. An injury of such a degree is followed by a process of repair which results in the formation of a normal type of polygonal epithelial cell which is of normal functional value. When such animals are reintoxicated by the same amount of uranium nitrate per kilogram, a secondary injury which may be of a severer nature than the initial injury develops and associated with it there is an increase above the normal value in the percentage concentration of phenoltetrachlorophthalein and a delay in the removal of the dye from the plasma. The repair process which has been accomplished by the formation of a normal type of cell has no acquired resistance to a secondary intoxication by this hepatotoxic substance. In other animals intoxicated by the same amount of uranium nitrate per kilogram a severer type of hepatic injury develops. This is more apt to occur in adult animals over six years of age. This order of injury as shown by a study of biopsy material consists in a marked accumulation in the epithelium of stainable lipoid material, edema of the cells and a more diffuse though not complete state of necrosis than that which occurs in those animals of the former group which have been described. With such a degree of epithelial injury the plasma concentration of phenoltetrachlorophthalein reaches a high level and the rate of its removal is proportionately delayed. A number of the animals with such a degree of hepatic injury fail to survive. Those effecting a survival repair the liver by the formation of an epithelium which is essentially different in its morphology from the normal polyhedral type of cell. Such a repair process originates in areas of severe liver damage characterized by a partial necrosis in which islands of hepatic tissue persist which are insufficiently injured to prevent the development of a process of repair. In such areas this process develops in a two-fold manner. The injured and ill defined cellular masses may increase in size through nuclear division and cell cytoplasm formation and remain as a syncytial mass from which buds develop and cord-like, imperfectly differentiated, epithelial structures grow into the general area of necrosis. In other locations there arise from injured epithelial tissue without the formation of a primary syncytial mass, cord-like structures which invade areas of epithelial necrosis in an irregular manner, though usually tending to converge towards the central vein of the lobules. This newly formed epithelium of repair is of a flattened type of cell structure which either shows imperfect cell differentiation or persists in syncytial formation. From such structures branching and budding of the epithelium may be observed with, not infrequently, bridges of nucleated epithelial

tissue connecting parallel cords of flattened liver cells. Between such cords of cells or syncytia are found greatly enlarged venous sinusoids.

The liver, the seat of such an abnormal type of epithelial repair process, retains its ability to remove phenoltetrachlorophthalein from the plasma. The initial plasma concentration of the dye is greater than occurs in animals with a normal type of epithelial repair and the rate with which the dye is removed is prolonged. When animals that have effected a repair to the liver by the formation of an atypical epithelium of this order are re-intoxicated with uranium nitrate in an amount in excess of that which induced a severe injury to normal hepatic epithelium, the abnormal type of cell is found to be resistant to this hepatotoxic agent as is shown by the failure of the cells to become severely injured or necrotic and by the maintenance of hepatic function as indicated by the ability of such cells to remove phenoltetrachlorophthalein from the plasma.

The reaction of the liver in terms of cell repair and acquired resistance is similar to that of the kidney as was indicated by such changes in the cells of the proximal convoluted tubule. A slight injury to such epithelial tissues is followed by a normal type of cell repair which has no acquired resistance. A severe injury prevents the normal type of repair process, the repair being accomplished by an atypical cell or by structures in syncytial formation which in the liver may be ascertained to be of functional value.

These observations would appear to have certain significant implications for they indicate that when an adult and differentiated tissue is so disturbed through injury that a normal type of cell repair becomes impossible, a repair process resulting in the formation of an embryonic type of tissue develops which not only acquires a resistance to injury greater than differentiated tissue but retains to a certain degree its normal functional value. Such an observation furthermore raises the question as to whether or not a sufficient degree of cellular injury can precipitate a type of cell repair which should be looked upon as a structural reversion of an ontogenetic order.

With the demonstration that following a uranium injury of a sufficient degree of severity a type of epithelial repair would develop which afforded resistance from secondary injuries from the same poison, the question naturally arose as to whether or not such an acquired resistance was specific or whether it was effective for other chemical agents with a demonstrated toxicity for hepatic epithelium. Many years ago it was shown by Whipple and Sperry¹⁶ that if a dog was starved for 24 hours and given chloroform by inhalation for one and one-half hours, there invariably developed a necrosis of the hepatic lobules involving one-half to two-thirds of their area. The following group of experiments have been conducted, with the above observations in mind, in order to ascertain if an atypical type of epithelial repair induced in the liver by a severe injury from uranium would afford the liver protection against the certainly acting hepatotoxic agent, chloroform when given to animals under the standard conditions as outlined by Whipple and Sperry. A group of young dogs were intoxicated

with 2 to 4 mg of uranium nitrate per kilogram. In such animals, as has been recorded, there develops a diffuse injury to the epithelium in which necrosis is not marked and which is characterized by fatty infiltration, granular degeneration and edema of the cells. There occurs a slight increase in the initial plasma concentration of phenoltetrachlorophthalein and usually some delay in the removal of the dye from the plasma. An injury of such an order of severity in young animals or puppies is followed by the development of a repair process which restores the liver to its normal structure. The epithelial repair is by a polyhedral type of cell. Such a process is completed within two weeks with a return of the liver to its normal functional value. When animals with this type of epithelial repair are starved for 24 hours and given chloroform by inhalation for one and one-half hours, there occurs a necrosis associated with fatty degeneration of the inner one-third to two-thirds of the hepatic lobules. The ability of the liver the seat of such an injury to remove phenoltetrachlorophthalein is definitely decreased.

When older animals are intoxicated by the same amount of uranium nitrate per kilogram or by an amount in excess of 4 mg per kilogram, there develops a severe and diffuse injury to the liver lobules in which epithelial necrosis is the most marked pathological characteristic. The epithelial repair process when it occurs following such a degree of injury, results in the formation of the usual atypical, flattened cells or of an epithelium syncytial in structure. The liver with this type of completed repair may have a normal functional value as shown by the use of phenoltetrachlorophthalein. When such animals are starved for 24 hours and given chloroform by inhalation for one and one-half hours, there fails to develop the characteristic central necrosis of the liver lobules. A fixed cell tissue resistance has been acquired on the part of atypical hepatic epithelium developing as a repair process to a severe injury from uranium nitrate, which has not only been shown by previous experiments to have a resistance for uranium, but also by these experiments to an entirely different chemical body, chloroform. Such an observation might warrant the assumption for the acquired resistance that the atypical cells of hepatic repair were unable to subject themselves to the action of chloroform in sufficient concentration to effect an injury. Even if this were true, such cells should be considered resistant if they maintained hepatic function. Such function is maintained by these cells as is indicated by their ability to regulate the plasma concentration of phenoltetrachlorophthalein and remove the dye from the plasma. Two factors apparently determine the degree of acquired resistance of such a type of repair process to chloroform: the duration of the preliminary period of starvation and either the concentration of chloroform in the liver or the length of time to which hepatic tissue is subjected to its action. If animals which have been starved for 24 hours and given chloroform for one and one-half hours with the demonstration of a complete hepatic resistance be later starved for 48 hours and given chloroform for three hours, a commencing

epithelial necrosis develops in the cells which have previously shown resistance in the location in the lobule where it should develop, centrally, around the central veins of the lobules. An acquired, fixed tissue cell resistance, like other forms of resistance, is relative and not absolute.¹⁷

Extending over a period of 14 years, a large number of animals have been used in this laboratory in which the liver was either primarily the object of investigation or in which it was subjected to study in conjunction with other organs and tissues. A rather large number of dogs have been observed which, on the basis of their age and certain associated physical defects, may be classified as senile animals. Such animals have varied in age from eight years to fifteen years and four months. Occurring in such a group of animals there has been found, at autopsy or by the removal of biopsy material, 26 dogs in which the liver has shown a diffuse change in its type of epithelium. The changes in these cells which have resulted in an altered structure of the liver resemble very closely those changes which may be induced experimentally by subjecting the liver to a severe intoxication by uranium nitrate which results in the development of an atypical type of epithelial repair. In these senile animals the epithelium shows very little evidence of cell differentiation but exists in the form of intensely staining syncytial cords, the irregularly placed nuclei of which are large in proportion to the surrounding cytoplasm and also stain deeply. Such cords are uniformly narrow and exhibit both branching and budding. More rarely, such structures end blindly by bifurcating into two cords of nucleated cytoplasm. Between such structures are to be found greatly enlarged venous sinusoids. These cords of epithelium are bizarre in their arrangement and fail to converge with any regularity toward the central veins of the lobule. When senile animals, that have been shown by a study of biopsy material to have an altered epithelial structure of the type described, are starved for 24 hours and given chloroform by inhalation for one and one-half hours, there fails to develop any evidence of cytological injury to such altered epithelium. The functional value of these cells, which may closely approach that of normal hepatic epithelium, fails to show any change in the rate with which it disposes of phenoltetrachlorophthalein. The cause for the formation of this atypical type of epithelium in the livers of senile animals is unknown. It has only been observed as a naturally acquired type of cell change in senile animals. In such senile dogs, similarly to those dogs in which this form of epithelium appeared as a repair process secondary to a severe hepatic injury, the embryonic, imperfectly differentiated, or clearly syncytial character of the epithelium appears to impart to this tissue resistance, while at the same time it retains its functional value in so far as one test for hepatic function is concerned. In the senile animals as was the case with the group of animals formerly described, the resistance to chloroform is not of an absolute value. If senile dogs which have shown resistance to chloroform as has been indicated above, be starved for a longer period and the duration of the chloroform anesthesia be increased, there develops evidence of epithelial

injury around the cential veins of the lobules. Usually from such a degree of injury there is no change either in the initial plasma concentration of phenoltetrachlorophthalein or in the rate with which it is removed from the plasma¹⁸

The question very naturally arises as to whether or not such cell metaplasias, which may be made to develop in the liver and the kidney as the result of injury and which may occur in the senile liver from some unknown cause and which show an acquired resistance, are permanent, or whether such cells may revert back to a normal type. This question can only be answered for a group of animals in which the liver was severely injured by uranium nitrate with the formation during repair of an atypical epithelium. At intervals after this type of cell was demonstrated to have appeared, histological studies of the liver were continued over several years by obtaining biopsy material which enabled any change in cell type to be observed. During these years of observation the animals were either reintoxicated by uranium or after a period of starvation subjected to the action of chloroform. In this relatively small group of animals the observation has been made that after periods which vary from a few months to approximately two years, the atypical, flattened type of resistant cell and in areas the syncytial structures show a reversion to a normal polyhedral type of cell. The rate with which such changes in cell reversion take place appears to depend on the age of the animal, occurring more rapidly in young animals than in adult and senescent groups. When animals which have shown such a partial reversion in cell type to or towards a normal order of polyhedral cell are starved and anesthetized with chloroform, such areas of cell reversion which are irregular in their distribution in the liver lobules give evidence of a loss in their acquired resistance in that changes of fatty degeneration appear in such cells followed by partial or complete necrosis. Three senile animals that have shown in the liver a change in epithelial type with an associated acquired resistance have been studied at intervals of three months over a period of eighteen months. During this time no indication of a reversion of these atypical cells to a normal type of cell has been observed¹⁹

SUMMARY

A review of the experimental work which has been presented in this discussion may with caution allow certain generalizations.

A sufficient degree of injury to specialized cells is usually followed by the formation of a functionally inactive tissue which though resistant to injury is of no value to organ function or the organism as a whole. A survey of different types of experimental procedures which have been employed in this investigation and which have extended over a period of years would indicate that for two organs, the liver and the kidney, a repair process may develop in their epithelial structure which is significant in that an altered, atypical type of cell is formed which is not only of functional

value but which is resistant to a changed organ environment in which it has to live and which is furthermore resistant to extraneous agents of a chemical character, certainly toxic for a normal type of cell. At present we have no method of such selectivity in its application that it will determine the functional value of resistant cells when they appear in the kidney as a reaction of repair. The function of such structure is so intimately related to glomerular function that a separation in the functional value of the two tissues becomes impossible. On the basis of experimental data, kidneys in which such an epithelial process has developed, associated with chronic glomerular damage, may have for months very slight interference in function and at the same time show a definite resistance to injury. The processes of repair resulting in such an acquired cellular resistance would appear to stabilize, for longer or shorter periods, renal function at a given pathological level of effectiveness and at the same time afford the kidney a certain degree of protection. Such tissue reactions would therefore be looked upon not as essentially degenerative and in this sense of no value, but as reactions which preserve a certain degree of function and at the same time impart resistance.

The studies of injury and repair which have been outlined in some detail for the liver on account of the structure of this organ, permit an evaluation of the degree of function possessed by the liver when different types of epithelial repair develop. These studies indicate that an abnormal type of epithelial cell may develop as a repair process, following a severe injury from uranium nitrate, which is not only resistant to uranium when used in an amount in excess of that necessary to injure normal epithelium but that such cells are also resistant to an entirely different substance, chloroform. This metaplastic epithelium of repair is of definite functional value and may even be of normal functional effectiveness as is shown by its ability to regulate the degree of concentration of phenoltetrachlorophthalein in the plasma and the rate with which this substance is removed from the plasma. The same type of statement may be made for the atypical epithelium which is found to occur naturally in the livers of certain senile animals. It is realized that these observations concerning an acquired, fixed cell resistance which may follow tissue injury and which have been observed to occur in senile animals are of a superficial nature. It is not inferred that a mere change in cell form is responsible for such states of acquired resistance. The assumption is made that associated with such changes in cell morphology, the finer, intracellular structure of such cells must be so changed and likely their chemical nature so modified that when they are subjected to a toxic agent in sufficient concentration to injure normal cells, such atypical cells either remain entirely resistant or their resistance is much greater than the normal order of cell which they have replaced. This inference is strengthened by the fact that when resistant, metaplastic cells revert to cells of normal configuration and acquire spe-

cialization in their internal structure, their ability to resist injury decreases or is lost

The atypical, flattened form of cell which has been described as offering in both the liver and the kidney resistance, is usually dispensed with by the assumption that such cellular modifications are an expression of cell atrophy and therefore represent a retrogressive change tending towards imperfect function, a lack of resistance and, ultimately, to an arrest in function in organ death. Such a conception of the significance of the cell types under consideration is entirely inadequate. It becomes difficult to conceive of atrophy, as such a state is usually interpreted, as occurring with new cell formation which is the case in the cell metaplasias under discussion. Atrophy as cell retrogression and degeneration develops in fixed cells from a variety of causes usually having a nutritional basis or as a pressure effect, and is essentially concerned at first with a modification in the configuration of existing cells and does not include in such a process new cell formation. Furthermore, the cell of atrophy is in general characterized by a definite diminution in function or the development of a functionless state, such states being associated with increased susceptibility to injury. The type of fixed cell of repair which has been the subject of discussion may be of normal functional value and yet manifest a definite resistance to injurious agents. Cells with such characteristics maintain life and should not be considered as primarily participating in a process which leads to organ dysfunction and death.

Of recent years, studies of the acquired resistance of tissues to injury have established certain facts which should be recorded in connection with the observations which have formed the basis for the present study. In 1927, Weller,²⁰ in his studies of the tolerance to lead as shown by the meningeocerebral manifestations of acute and subacute lead poisoning, came to the conclusion that an actual, acquired tolerance to this metal developed in the guinea pig on the part of such tissues. Very recently Sprunt,²¹ in a study of "Simple Atrophy of the Liver" in human material, has observed the development of the same type of altered, metaplastic cell which has been described as occurring in the liver of dogs as a reaction of repair and in certain senile animals. He states that "although the conclusions drawn in this paper are based on an analogy between certain morphological changes in the human liver and those in the dog, it is believed that further study will show that these changes in man are, as they are in the dog, associated with a changed physiological response." Observations of a somewhat similar nature on the acquired resistance of fixed tissue cells to injury have been made by Hunter²² who was able to induce in rabbits a resistance to bichloride of mercury following an injury from this substance which resulted in the development of an atypical repair process to the tubular epithelium of the kidney and by Smyth, Smyth and Carpenter²³ who observed an acquired resistance on the part of hepatic epithelium to carbon tetrachloride when used for purposes of secondary intoxication. Prior to the observation of

Hunter on the acquired resistance of renal epithelium to bichloride of mercury, Havill, Lichty, Taylor and Whipple,²¹ in a study of the disposition of hemoglobin by the dog kidney, observed in certain of their animals that had been given hemoglobin close to the renal threshold value with the accumulation of pigment granules in the epithelial cells of the convoluted tubules that such dogs would tolerate the normal minimal lethal dose of bichloride of mercury with little if any evidence of injury to the tubular epithelium. Very recently Olitsky, Sabin and Cox²² have observed that young mice are more susceptible than older ones to a nasal inoculation by a specific virus and furthermore that this difference was not due to the presence of antibodies in the older mice as such animals were not immune to intracerebral inoculation. The point of resistance or blockage to the invasion of the virus would therefore appear to be in the nasal mucous membrane of mice of different age periods. In a later paper by Sabin and Olitsky,²³ observations of the above order have been confirmed and amplified. They conclude in part that "the resistance of old mice to peripheral inoculations of vesicular stomatitis virus appears to be the result of (a) changes produced by age not in the whole animal but in certain specific, isolated structures, and (b) the special mode of dissemination of peripherally injected virus." From this very brief review of work which has been accomplished on localized cell resistance it would appear that such a state may express itself when a variety of agencies are employed in an attempt to injure tissues.

The studies of an acquired fixed cell tissue resistance developing as a process of cell metaplasia secondary to tissue injury which have been discussed as emanating from this laboratory along with other observations of a confirmatory nature, would indicate that changes in the morphology of fixed tissue cells, with an assumed change in their chemical constitution, play a significant part in certain types of tissue resistance. The association of the age factor in the development of such a resistance is important, not only in prolonging through cell resistance the state of senescence but also in terms of the influence which fixed cells at different age periods may exert on the development of certain infectious diseases, both as a local tissue reaction and as more generalized invasions of the tissues of the host. Finally, this type of acquired resistance on the part of cells following injury may aid in filling in certain gaps in our understanding of tissue resistance as an acquired immunity which can not be satisfactorily explained either on a humoral (antibody) basis or in terms of the activity of wandering cells. These studies as a whole impress one with the lack of fixity on the part of cells which are supposed to be static and fixed, at least in their morphology. They suggest that change in configuration and, likely, in chemical constitution are essential characteristics of cell life and, furthermore, that such changes may not only be dependent upon injury and a tissue reaction of repair but may be due to the aging process expressing itself cytologically in organ life as well as in the organism as a whole.

BIBLIOGRAPHY

- 1 MACNIDER, W DEB The pathological changes which develop in the kidney as a result of occlusion by ligature of one branch of the renal artery, *Jr Med Res*, 1910, *xv*, 91-94
- 2 MACNIDER, W DEB The pathological changes which develop in the kidney as a result of occlusion by ligature of one branch of the renal artery Part II Conclusion, *Jr Med Res*, 1911, *xi*, 425-454
- 3 MACNIDER, W DEB A note on the regeneration of renal epithelium in the intact cat kidney, *Jr Med Res*, 1911, *x*, 369-372
- 4 KAUFMAN, E *Lehrbuch der speziellen pathologischen Anatomie für Studierende und Ärzte*, Berlin, O Reimer, 6 Aufl, Band, 1911, 815-818
- 5 MACNIDER, W DEB A study of the renal epithelium in various types of acute experimental nephritis and of the relation which exists between the epithelial changes and the total output of urine, *Jr Med Res*, 1912, *xxi*, 79-126
- 6 MACNIDER, W DEB The inhibition of the toxicity of uranium nitrate by sodium carbonate, and the protection of the kidney acutely nephropathic from uranium from the toxic action of an anesthetic by sodium carbonate, *Jr Exper Med*, 1916, *xxiii*, 171-187
- 7 CHITTENDEN, R H, and HUTCHINSON, M T Some experiments on the physiological action of uranium salts, *Trans Conn Acad Arts and Sci*, 1888-1892, *viii*, 1
- 8 SUZUKI, T *Morphologie der Nierensekretion*, Jena, 1912
- 9 MACNIDER, W DEB On the difference in the response of animals of different ages to a constant quantity of uranium nitrate, *Proc Soc Exper Biol and Med*, 1914, *xi*, 159-162
- 10 MACNIDER, W DEB A consideration of the relative toxicity of uranium nitrate for animals of different ages, *Jr Exper Med*, 1917, *xxvi*, 1-17
- 11 MACNIDER, W DEB The development of the chronic nephritis induced in the dog by uranium nitrate A functional and pathological study with observations on the formation of urine by the altered kidneys, *Jr Exper Med*, 1929, *xl*, 387-409
- 12 MACNIDER, W DEB Urine formation during the acute and chronic nephritis induced by uranium nitrate, *Harvey Society Lecture*, Baltimore, 1928-1929
- 13 MACNIDER, W DEB The functional and pathological response of the kidney in dogs subjected to a second subcutaneous injection of uranium nitrate, *Jr Exper Med*, 1929, *xl*, 411-433
- 14 MACNIDER, W DEB The development of an acquired resistance to bichloride of mercury by renal epithelium in the proximal convoluted tubule, *Proc Soc Exper Biol and Med*, 1937, *xxxvii*, 90-91
- 15 MACNIDER, W DEB The liver injury induced by uranium nitrate A consideration of the type of epithelial repair which imparts to the liver resistance against subsequent uranium intoxications, *Jr Pharm and Exper Therap*, 1936, *lv*, 359-372
- 16 WHIPPLE, G H, and SPERRY, J A Chloroform poisoning, liver necrosis and repair, *Bull Johns Hopkins Hosp*, 1909, *x*, 278-289
- 17 MACNIDER, W DEB The resistance of liver epithelium altered morphologically as the result of an injury from uranium followed by repair to the hepatotoxic action of chloroform, *Jr Pharm and Exper Therap*, 1936, *lvi*, 373-381
- 18 MACNIDER, W DEB The resistance to chloroform of a naturally acquired atypical type of liver epithelium occurring in senile dogs, *Jr Pharm and Exper Therap*, 1936, *lvi*, 383-387
- 19 MACNIDER, W DEB Concerning the persistence of an acquired type of atypical liver cell with observations on the resistance of such cells to the toxic action of chloroform, *Jr Pharm and Exper Therap*, 1937, *lvii*, 393-400
- 20 WELLS, C V Tolerance in respect to the meningeocerebral manifestations of acute and subacute lead poisoning, *Arch Int Med*, 1927, *xxix*, 45

- 21 SPRUNT, D H Simple atrophy of the liver Its relation to increased resistance, Arch Path, 1937, *xiv*, 738-742
- 22 HUNTER, W C Experimental study of the acquired resistance of the rabbit's renal epithelium to mercuric chloride, ANN INT MED, 1929, *xi*, 796-806
- 23 SMYTH, H F, SMYTH, H F, JR, and CARPENTER, C P The chronic toxicity of carbon tetrachloride, animal exposures and field studies, Jr Indust Hygiene and Toxicol, 1936, *viii*, 277
- 24 HAVILL, W H, LICHTY, J A, JR, and WHIPPLE, G H III Tolerance for mercury poisoning increased by frequent hemoglobin injections, Jr Exper Med, 1932, *lv*, 627
- 25 OLITSKY, P K, SABIN, A B, and COX, H R An acquired resistance of growing animals to certain neurotropic viruses in the absence of humoral antibodies or previous exposure to infection, Jr Exper Med, 1926, *lxiv*, 723
- 26 SABIN, A B, and OLITSKY, P K Influence of host factors on neuroinvasiveness of vesicular stomatitis virus III Effect of age and pathway of infection on the character and localization of lesions in the central nervous system, Jr Exper Med, 1938, *lxvii*, 201

PROGNOSIS AND TREATMENT OF ERYSIPELAS ¹

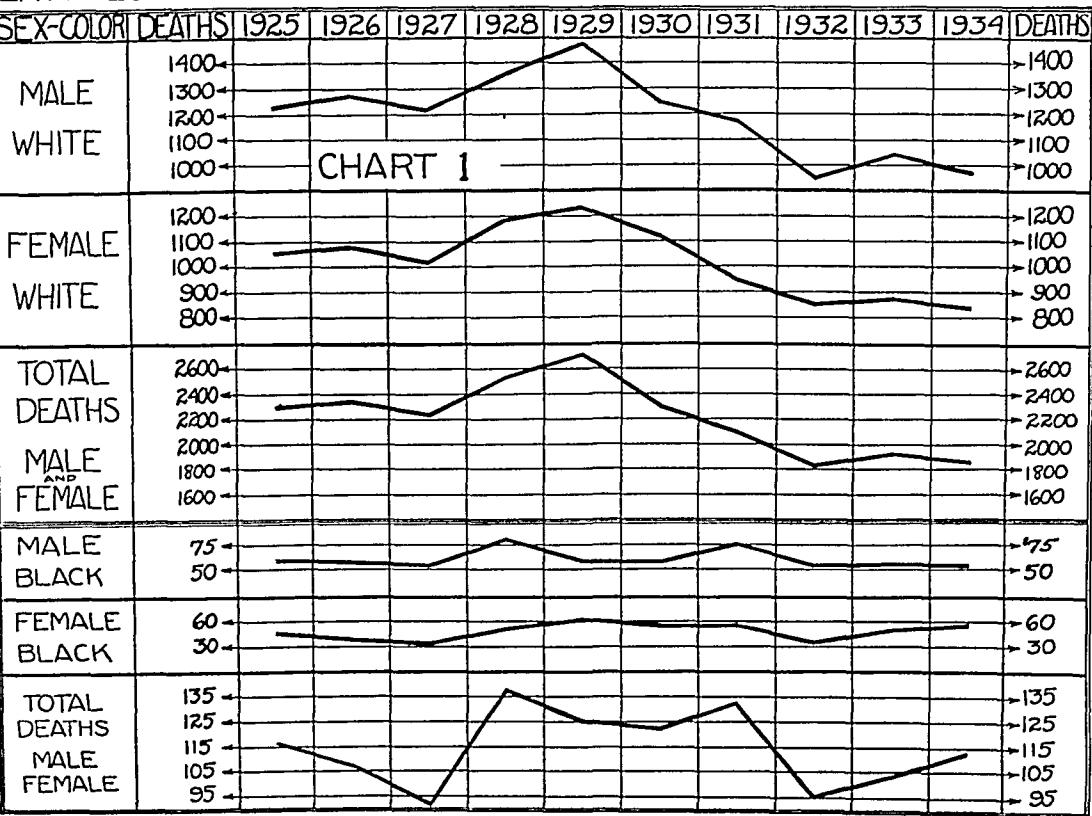
By JOHN A TOOMEY, M D , F A C P , *Lakewood, Ohio*

MORTALITY statistics are the only sources of factual information not affected by the personal equation

From 1912 to 1933, Hoyne in Chicago had a mortality rate of 12.47 per cent in 5,666 cases of erysipelas, from 1929 to 1933, it was 13.4 per cent in 1,193 cases. From 1927 to 1931, Gordon and Young ¹ in Detroit had 1,156 cases with a mortality rate of 9.5 per cent. In Bellevue Hospital, in New York City, from 1904 to 1937, there were 15,277 cases with a mortality rate of 10.1 per cent ². Symmers ² stated that in 3,311 cases admitted to the same institution in subsequent years and treated with antitoxin, the mortality rate was lowered to 7.1 per cent.

A curve of the total number of deaths from erysipelas in the registered areas of continental United States ³ for 10 years (1925 to 1934, inclusive) is shown in chart 1. Antitoxin was introduced in 1926. There was a

ERYSIPELAS MORTALITY~ SEX AND COLOR~ UNITED STATES 10 YEARS

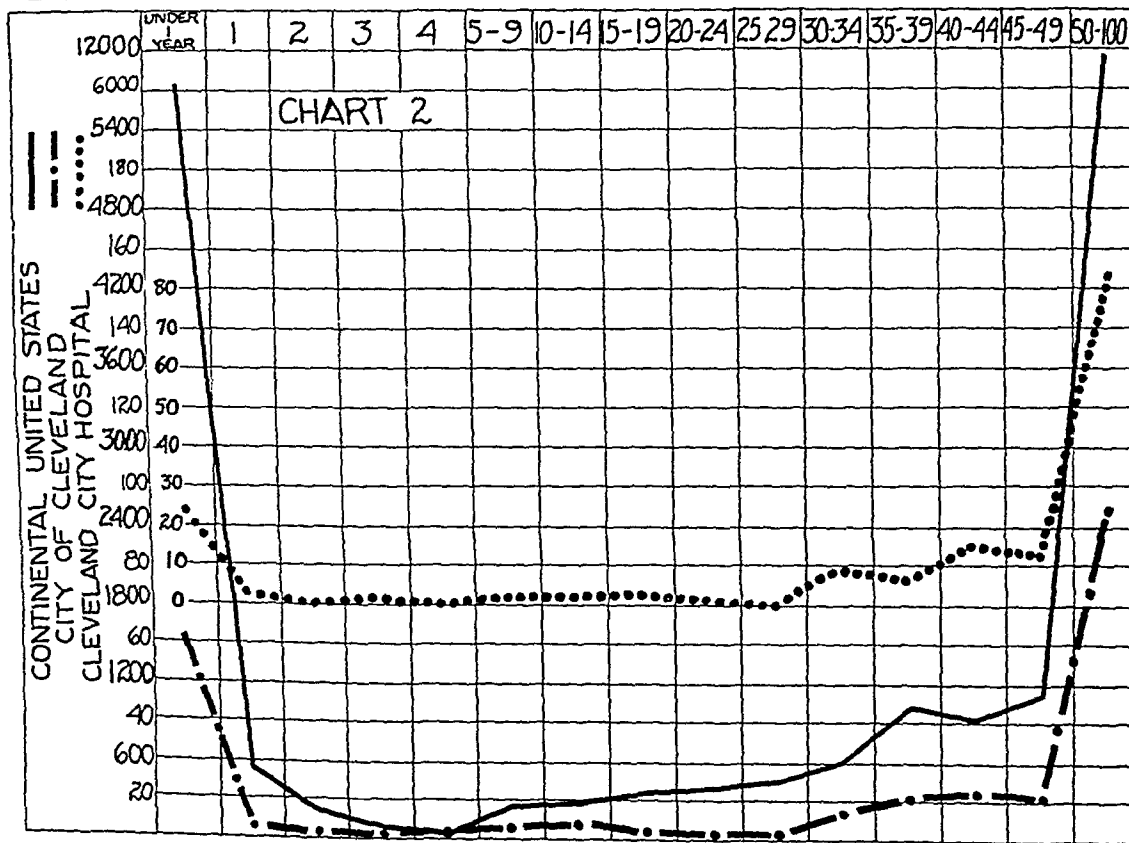


* Delivered before the American College of Physicians, New York City, April 6, 1938
From the Department of Pediatrics, Western Reserve University, and the Division of Contagious Diseases, City Hospital, Cleveland, Ohio

sharp rise in total mortality for the white race in 1928 and 1929 with a drop in 1930 and 1931, and a comparatively level period for the next two years. The mortality for the Negro race was $\frac{1}{20}$ that of the morbidity rate, although their population was nearly $\frac{1}{10}$ that of the white race. There was a rise in their total mortality in 1928 with a sustained high level in total cases to 1931, followed by a drop and a gradual rise again in 1933 and 1934.

It can be seen from chart 1 that less women die than men, both among the white and black races. The difference, although definite, is not extraordinary and might even be less apparent were the total morbidity known as well as the total mortality.

ERYSIPELAS MORTALITY - TOTAL AGE DISTRIBUTION FOR 10 YEARS



When statistics for the five years from 1925 to 1929 obtained from the Department of Commerce are examined, it is found that in the United States 3,654 deaths, or over 28 per cent of the total mortality from erysipelas during these years, occurred during the first year of life. Five thousand seven hundred and eighty-three deaths, or over 45 per cent of the total mortality, occurred in patients over 50 years of age. In short, 73 per cent of the total deaths occurred in the extremes of life. Between the ages of 10 and 50, there were 2,690 deaths, or 21 per cent of total deaths. It may be concluded that general mortality rates even without benefit of comparative morbidity rates confirm the impression that the mortality for adults between the ages of one and 50 years is comparatively low.

Conclusions cannot be drawn from statistics obtained from hospital case records unless the hospital's morbidity and mortality rates are compared with the total morbidity and mortality rates of the community in which the hospital is located. Such statistics were available for certain years, curves representing the total morbidity for 10 years (1925 to 1934, inclusive) have been drawn for the nation, the City of Cleveland, and Cleveland City Hospital (chart 2). The lines of the three curves tend to be roughly parallel.

In chart 2, attention should be called to the height of the lines representing deaths in infancy. Objection may be made, and rightly so, to the sharp rise in the curve as representative of the older age groups, i.e. from 50 to 100 years. The reason for this is because ages from 50 to 100 years were grouped together.

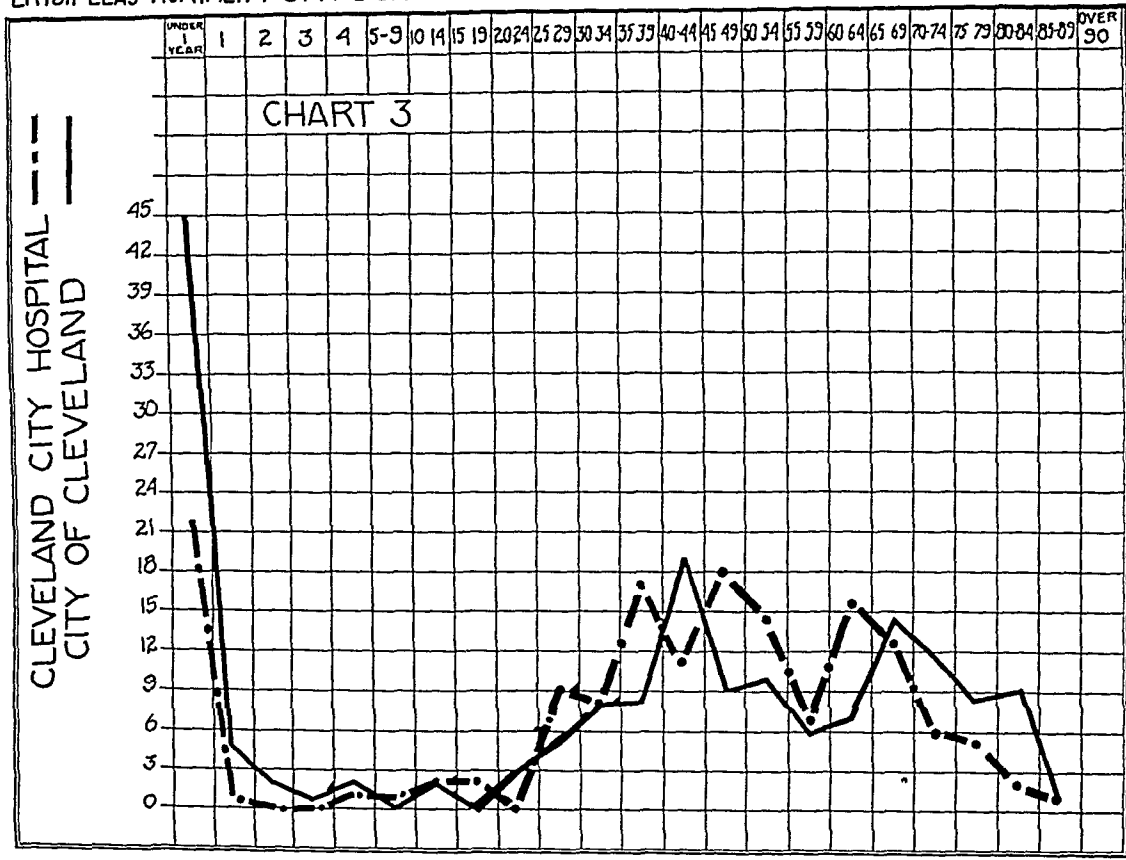
When the older age groups for the City of Cleveland and Cleveland City Hospital are split up as in chart 3, and the total deaths after the fifth year of life are grouped in five year periods, the curves for the later years rise, but are not so precipitous. Charts 2 and 3 show that age is a predisposing factor only in infancy. It is not clear that age in itself has anything to do with a total increase in deaths in later years. In fact, it is easy to show that it is not age itself, but conditions coincident with the aging process in human beings which predispose these individuals to a higher mortality.

These facts become even more obvious when a chart is made to show percentage mortality per 100,000 by age groups for Cleveland and Continental United States (chart 4).

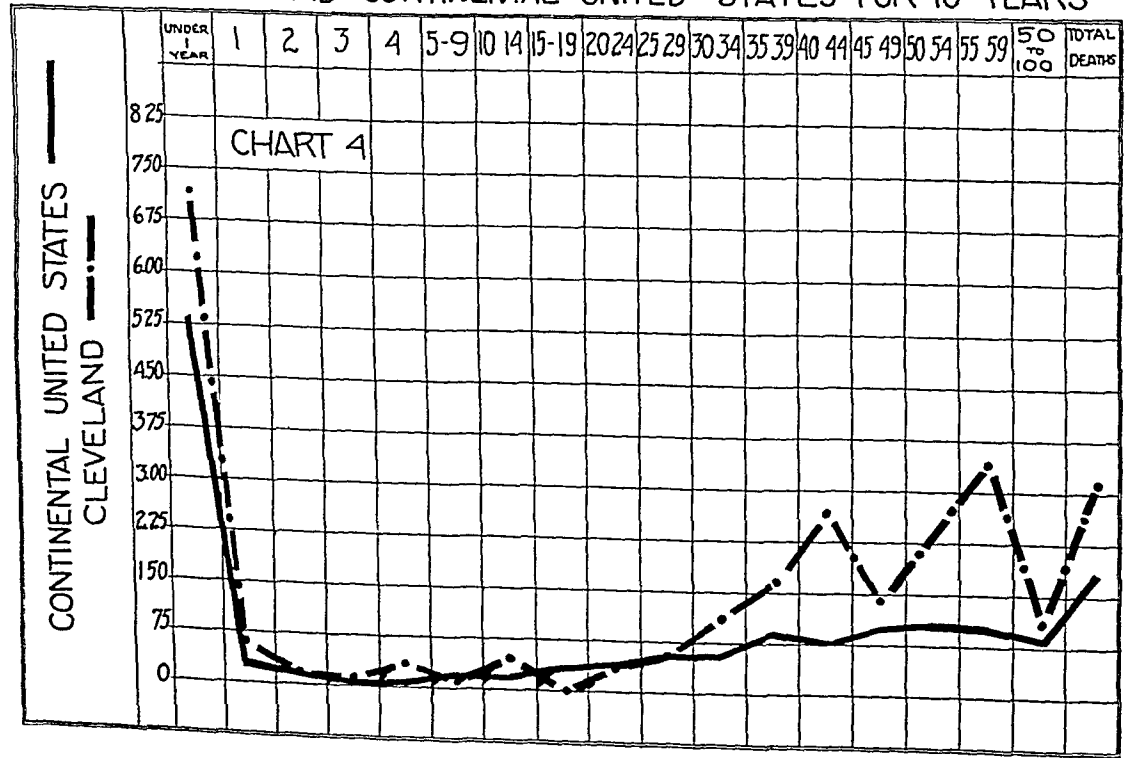
A most informative graph was drawn from data secured on the erysipelas mortality rate per 100,000 for Continental United States (chart 5). The figures quoted by Birkhaug⁴ are used for the years 1906 to 1927, inclusive. Computations for the succeeding years 1928 to 1934 are made by using estimated population figures. Even allowing for gross errors, it will be noted that the total mortality rate per 100,000 has been falling even before the introduction of recent therapies—a greater fall before 1927 than afterwards. The figures for the yearly fall are not known, but roughly the curve would seem to have a gradual downward trend, reaching an even low in 1932.

General averages give erroneous impressions and inaccurate conclusions may be drawn when only the total death rates are examined. A curve of per cent mortality of age groups and total number of cases in each group for the City of Cleveland for the years 1925 to 1929 inclusive has been drawn in chart 6. The mortality rate for infants under one year was 49.4 per cent, between one and two years, 11.1 per cent, between two and three years, 6.6 per cent, between three and four years, 5.8 per cent, and between four and five years, 7.1 per cent. For the entire group from one to five years of age, it was 27.1 per cent. It can be seen that a sharp drop in percentage mortality occurs in the groups between 5 and 30 years of age, for although there were 236 cases there were only eight deaths, a mortality

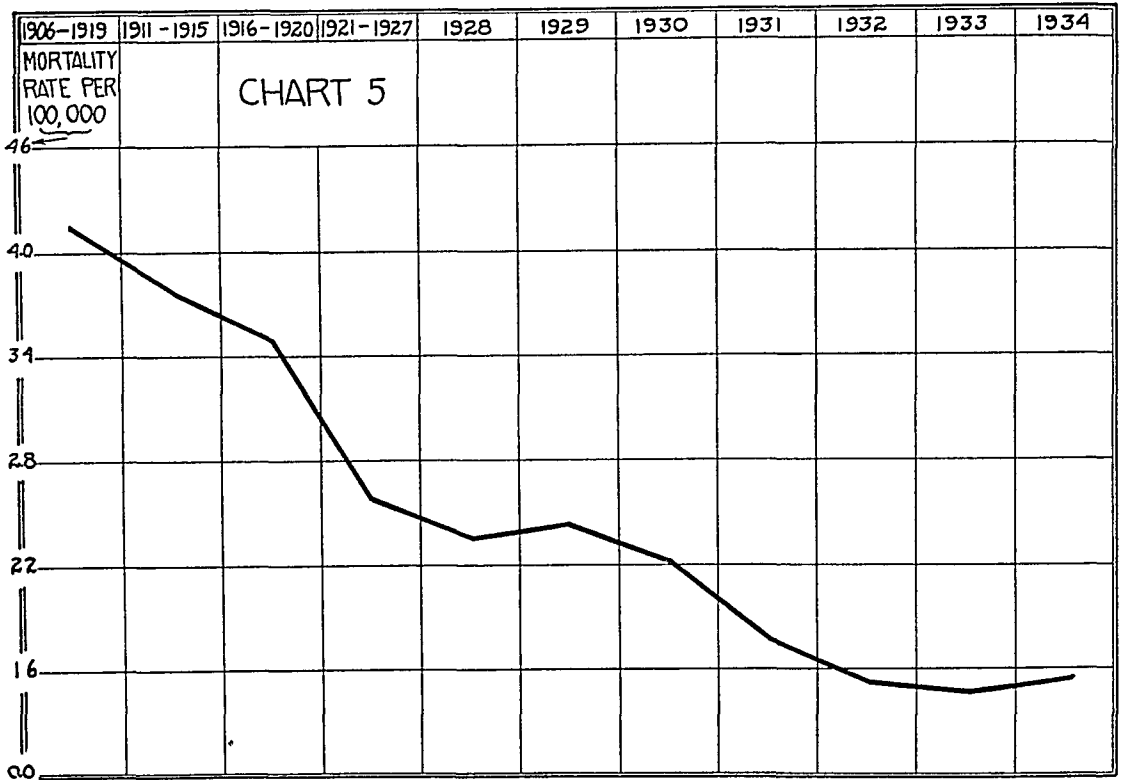
ERYSIPELAS MORTALITY BY AGE GROUPS CLEVELAND 5 YEARS AND CLEVELAND CITY HOSPITAL 10 YEARS



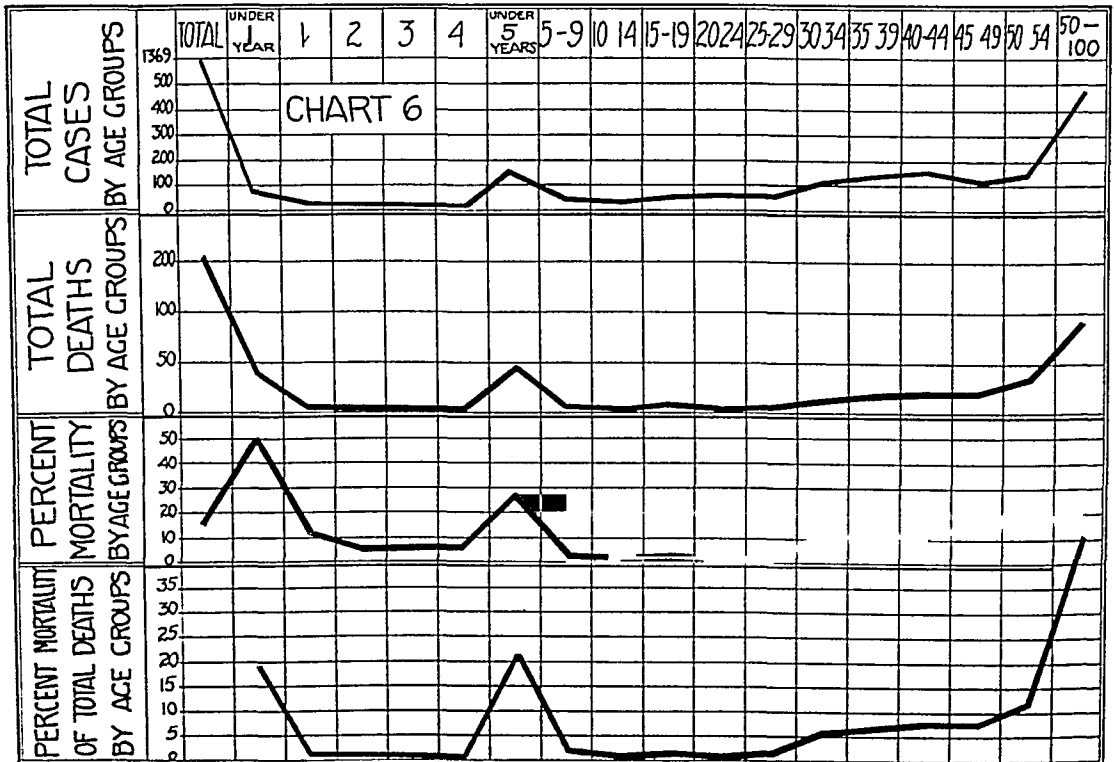
ERYSIPELAS PERCENT MORTALITY PER 100,000 BY AGE GROUPS FOR CLEVELAND AND CONTINENTAL UNITED STATES FOR 10 YEARS



ERYSIPELAS MORTALITY RATE PER 100,000 ~ CONTINENTAL UNITED STATES



ERYSIPELAS CLEVELAND 1925-1929--- CASES AND DEATHS BY AGE



rate of 3.3 per cent. Percentage mortality rises markedly for the older age groups. Few patients between the ages of 5 and 30 years die of erysipelas. It is evident that if the advantages for recovery that age seems to confer are ignored, and the treated cases are considered as a whole, statistics become meaningless. It might be stated as an axiom that as a rule a normal healthy young adult who contracts erysipelas always recovers.

Referring again to the statistics of Cleveland for the years 1925 to 1929, inclusive, it will be found that the mortality rate in infants under one year of age with reference to case incidence was 49.4 per cent, but the mortality rate of this group with reference to the total number of deaths was only 19.5 per cent. The case mortality rate of the age group, 5 to 49 years inclusive, was 9.7 per cent, but 31.4 per cent of the cases that died were in this group. The same is true of the old age group (from 50 to 100 years of age) the mortality rate was 19.8 per cent of the cases in that age group, although this represented 44.7 per cent of the total number of cases which died in this series.

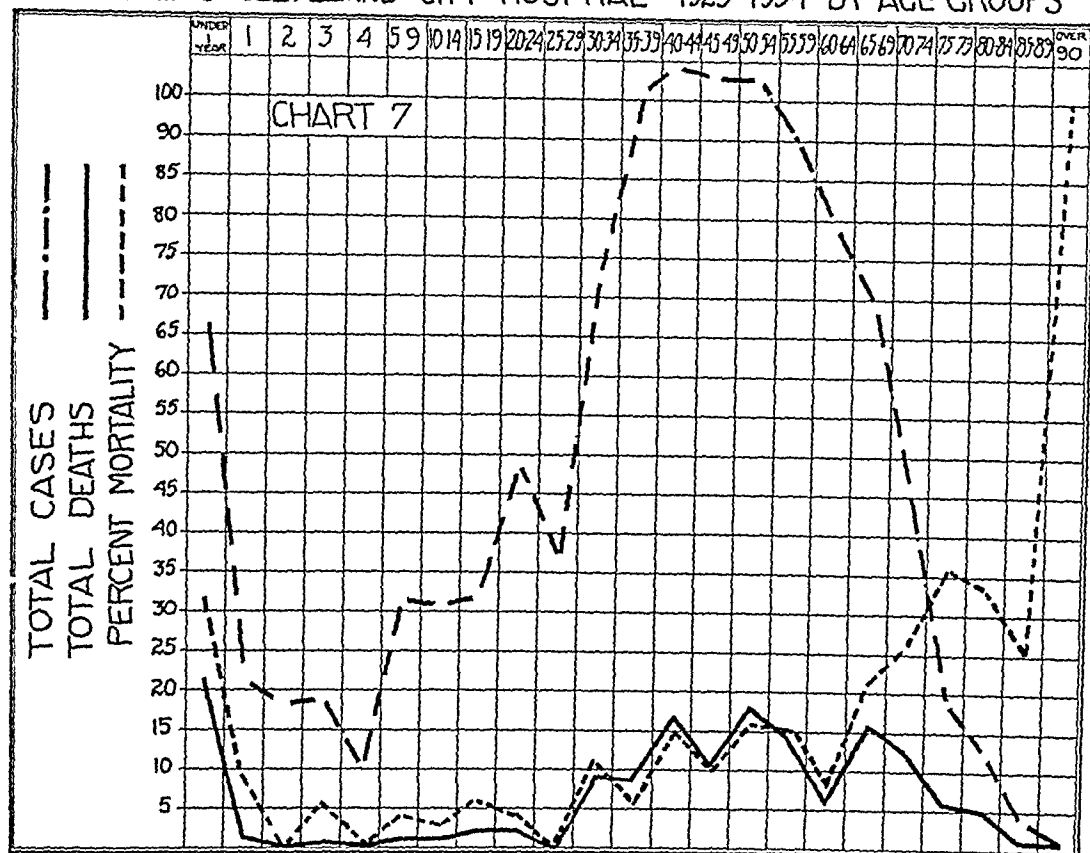
For the first five years of life, the number of deaths is approximately the same in both males and females of the black and white races. The fact that males in later life are more liable to contract erysipelas than females is probably due to increased chances of exposure and irritation. The average mortality rate in these years was 26.9 per cent for white males, 28 per cent for white females, 41 per cent for Negro males and 25 per cent for Negro females. The 41 per cent for Negro males is comparatively high but this percentage difference was more apparent than real, it was not significant since the number of cases in this group was so few that a few cases one way or another would make a marked change in the percentage rate.

In chart 7, curves for the total deaths and cases, and the percentage mortality are drawn. It shows clearly the chances of survival in the various age groups.

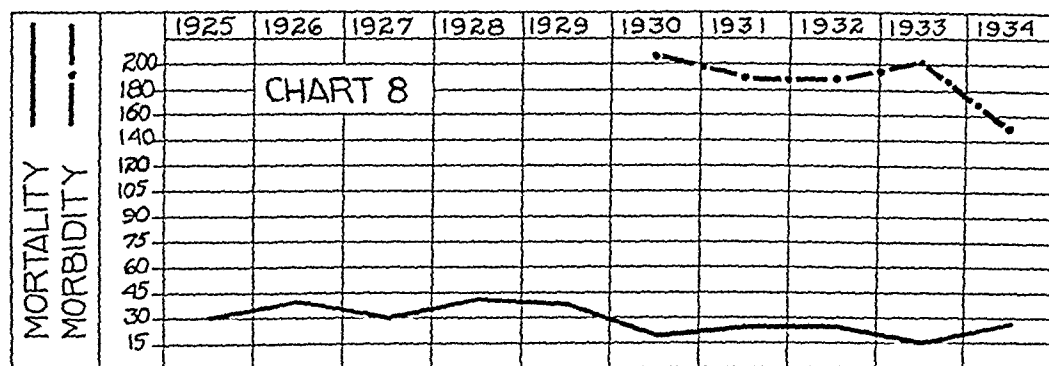
In chart 8, the morbidity curves for five years and the total mortality for 10 years for the City of Cleveland are drawn, while the morbidity and mortality rates are drawn for the Cleveland City Hospital for a 10 year period. The most important information gained from this chart is that the mortality of the hospital treated cases has remained about the same from 1932 to 1937, inclusive, although there was a drop in the total mortality for the hospital and the City of Cleveland in 1934. It showed also that the hospital has in some of the later years treated most of the cases that died in the community. The total number of deaths has dropped in the city since 1930, but the total number of hospital deaths has been rising since 1932. An increase in the hospital mortality rate means little if the total mortality rate of the community does not rise also.

Erysipelas may be the *coup de grace* that ends a long battle against some unrelated infection or degenerative organic condition, or merely an infectious episode experienced and recovered from long prior to the ultimate battle for existence. If to these possibilities are added the fact that the mortality and morbidity rates vary for different seasons of the year and

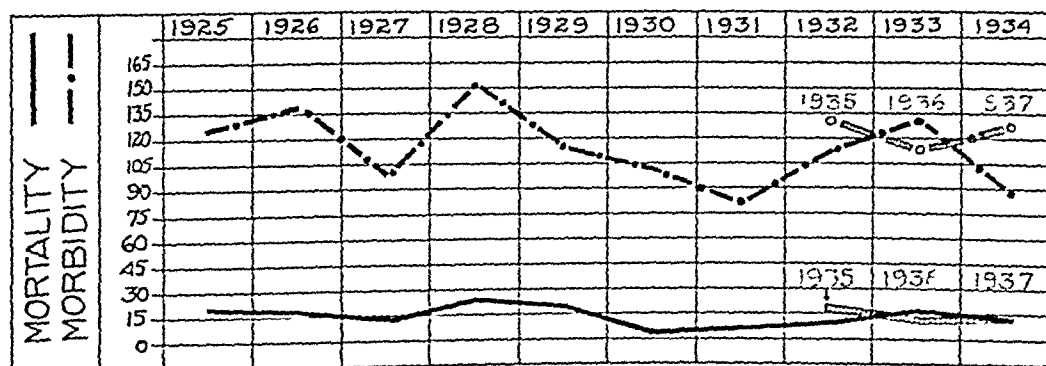
ERYSIPELAS CLEVELAND CITY HOSPITAL~1925-1934 BY AGE GROUPS



ERYSIPELAS MORTALITY AND MORBIDITY~CLEVELAND . 10 YEARS



ERYSIPELAS MORTALITY AND MORBIDITY~CLEVELAND CITY HOSPITAL 13 YEARS



for different years as well, and that the erysipelas may be caused by organisms other than the streptococci (pneumococcus, *B coli*, *B typhosus*, staphylococci, etc.), then it can be seen how difficult it sometimes becomes to draw conclusions about therapeutic procedures from statistics

Why do people die from this disease? When the records of the patients who died at Cleveland City Hospital during the period from 1925 to 1937, inclusive are studied, it is found that those who died were (1) infants under one year of age, especially those with vulval or abdominal erysipelas (Group I), (2) patients over 50 years of age (Group II). (3) patients with pulmonary disease, such as tuberculosis, bronchopneumonia and lobar pneumonia (Group III), (4) patients with chronic organic disease such as chronic myocarditis, valvulitis or arteriosclerotic disease (Group IV), (5) patients with concomitant acute infections such as influenza and other infectious or contagious diseases (Group V), (6) patients who had a severe debilitating illness immediately before the attack of erysipelas (Group VI), (7) patients with acute or chronic alcoholism (Group VII), (8) patients who had suffered some injury (Group VIII) Not all patients in these groups died, but all of the patients who died belonged to one of these groups Only two patients died simply from erysipelas They were both obese women with questionable pulmonary involvement Those who were not in these categories recovered, regardless of how many attacks of erysipelas they had had, or how often the lesions had spread, or what kind of therapy was used Thus, when good results are considered, those cases that fall outside the categories mentioned should be excluded

GROUP I

Infants under One Year of Age
34 of 218 deaths (1925 to 1937, inclusive)
Cleveland City Hospital

Anemia, secondary	Otitis media, suppurative
Bronchopneumonia	Osteomyelitis
Cellulitis	Peritonitis
Fracture, skull	Prematurity
Malnutrition	Sepsis
Mastoiditis, bilateral	Septicemia
Meningitis	Syphilis, congenital
Nephritis, acute	Thrombosis, sinus

GROUP II

Patients over 50 Years of Age with Complications
80 of 218 deaths (1925 to 1937, inclusive)
Cleveland City Hospital

Abscess, lung	Emphysema	Nephritis, chronic
Abscesses, multiple	Furunculosis	Panophthalmitis
Aneurysm	Gangrene	Paralysis agitans
Arteriosclerosis	Heart disease, passive	Paresis, general
generalized	congestive	Pericarditis, adhesive,
Arthritis	Hemorrhage, cerebral	chronic
Ascites	Hypertension	Psychosis, Korsakoff's
Asthma	Hypertrophy, prostate	Sclerosis, coronary
Bronchopneumonia	Infarct, lung	Septicemia
Carcinoma	Insufficiency, myocardial	Syphilis, tertiary
Cirrhosis, liver	Jaundice, toxic	Tuberculosis, kidney
Dementia, senile	Lymphangitis	Ulcer, duodenal
Diabetes	Myocarditis	Uremia
Edema, lungs	Nephritis, acute	Valvulitis, cardiac

GROUP III

Patients from 1 to 50 Years of Age (Mostly over 30 Years)
37 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

Pulmonary Tuberculosis (4), Bronchopneumonia and Lobar Pneumonia (33)

GROUP IV

Patients from 1 to 50 Years of Age with Chronic Diseases
15 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

Anemia, secondary	Pericarditis, adhesive and pleurisy,
Diabetes	chronic with pneumothorax
Elephantiasis	Osteomyelitis
Heart disease, rheumatic (5)	Silicosis
Hepatitis, toxic	Stricture, urethral
Nephritis, chronic	Ulcer, peptic and vascular disease, diffuse

GROUP V

Individuals from 1 to 50 Years of Age with Other Acute Infections or Conditions
35 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

Abscess, brain	Lymphadenitis, suppurative
Abscesses, multiple	Mastoiditis
Agranulocytosis	Meningitis
Arthritis, septic	Osteomyelitis
Cellulitis	Peritonitis
Cystitis	Pertussis
Dysentery	Pyelitis
Empyema	Retention, acute urinary
Fistula, pulmonary, post traumatic	Rubeola
Gas bacillus infection	Scarlet fever previous to erysipelas (3)
Glossitis, acute	Septicemia
Influenza	Serum sickness

GROUP VI

Cases up to 50 Years of Age with Previous Severe Infections
4 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

Abscess, peritonsillar with streptococcus sore throat, influenza, pertussis, pneumonia

GROUP VII

Adults up to 50 Years of Age with Delirium Tremens
6 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

One case developed a psychosis, escaped from the hospital, returned and died as a result of exposure. He also had serum sickness

GROUP VIII

Cases with Erysipelas Secondary to an Accident
4 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

The types and kinds of complications are listed. Specific forms of treatment might be instituted because of the erysipelas in the infants (Group I) and in individuals with pulmonary and acute infections (Groups

III and V), and some decrease in mortality might be expected. A close study of the complications in other groups, however, makes us realize that they themselves may have created conditions very difficult to overcome. Most cases of erysipelas have a history of a previous acute or chronic upper respiratory infection immediately preceding the erysipelas, or a previous localized infection which has been irritated. The pneumonia which may develop often did not need the erysipelas to start it, being already present, and the erysipelas merely speeded up the exit.

Thus, in order to make a prognosis, one needs the information obtained from a history that has been carefully taken and a physical examination that has been meticulously performed.

PART II TREATMENT

The value of any remedy for erysipelas should be gauged by its ability to save the patients who fall in those groups who usually die, the other patients get better anyway.

Prior to 1926, the treatment of this disease was anything but specific. Most endeavors were directed toward making the patient comfortable and watching for complications. In May 1926, Birkhaug⁵ introduced erysipelas antitoxin. Various reports appeared. It was claimed that with the use of antitoxin the general appearance of the patient became better, the temperature and pulse rate dropped, the length of time the patient was ill was decreased, there were no extensions, the toxicity definitely diminished. Within from 12 to 18 hours after injections, there was a rapid disappearance or fading of the lesion and absorption of the pitting edema, and that the mortality rate was decreased. It is very difficult to evaluate statistics, but it should be easy to duplicate these experiences.

My report on therapy is only preliminary, but sufficiently complete to enable me to state that our patients have not responded in like manner. Cases of uncomplicated erysipelas that have merely a localized lesion without extensions are ill from about 2 to 14 days. The average is about seven days. The majority of our cases and the controls in our series that recovered began to show improvement between the fifth and eighth days. Unless some complications arise, it is unusual for the patient to be acutely ill longer than for this length of time. When spreads occur, it may take as long for the new lesion to clear up as did the original one. Many cases are not sick for even five or eight days.

In a study of 115 cases, McCann⁶ concluded that antitoxin had no effect on the duration of fever and that the average stay in the hospital was not less in his serum treated group. He felt that a true objective examination for comparisons could only be made by studying the temperature charts.

Thus far, we have treated 520 cases between 1929 and 1938 with erysipelas antitoxin and have had 1313 untreated control cases—755 from

1922 to 1929 and 558 from 1929 to 1938. Our cases have been treated with antitoxins purchased from various biological laboratories.

Serum sickness has occurred in a little more than 9 per cent of the cases. More than one dose of antitoxin was given to 239 patients as there was no clinical improvement after the intramuscular injection of one ampoule of antitoxin. Fifty-eight per cent of the total number of treated cases had extensions. The total mortality rate was 13 plus per cent. Thirty-five per cent of the untreated cases had extensions, and the mortality rate was 15.5 per cent. Infants seemed to derive some benefit from the use of antitoxin, as the mortality rate was decreased, confirming the results of Eley⁷ and Blackfan⁸. In adults, however, the use of antitoxin did not lessen the number of hospital days. It did not cause an immediate decrease in the temperature curve or pulse rate, and in my experience, did not prevent the spread of the lesions of erysipelas.

The benefits that result from the use of newly discovered therapies are sometimes so obvious that control cases seem unnecessary. This is not true of erysipelas antitoxin. It was true, however, of diphtheria antitoxin when it was first introduced. From our experience with sulfanilamide in the treatment of erysipelas, it is believed that it is also true of this drug.

Approximately 50 cases were treated experimentally with antitoxin and various amounts of Prontylin (sulfanilamide) before we finally came to treat erysipelas with this drug alone. All cases, save those with hepatitis, increasingly severe nephritis or sensitivity to sulfanilamide are now being treated in the following way. The dose for the first 24 hours is computed on the basis of 1 gram of sulfanilamide per pound body weight. One half of the total dose is given at once and the other half is given in divided doses over the first 24 hour period. Each succeeding day, until the drug is discontinued, the patient is given $\frac{1}{2}$ gram per pound body weight. All but two patients have received this drug by mouth, and infants and patients in delirium are given it by stomach tube. Two patients were injected with the drug subcutaneously. When the drug was injected subcutaneously, 75 grams (5 grams) were added to 625 c.c. of saline, and the whole given as an infusion. All such doses are modifications of those suggested by Long and Bliss⁹. Rarely need this drug be given for more than four days unless there are local abscesses in addition to the erysipelas. Blood counts and hemoglobin estimations must be done daily and as soon as 400 grams have been given, the patient should be carefully reexamined.

With antitoxin the results were questionable save in the infant group. With sulfanilamide, they seem definite. Seventy-two of 76 cases thus treated with the latter have recovered and 3 have died, a mortality rate of 4 per cent. One of the cases that died was a 58 year old arteriosclerotic male who had been cured of erysipelas with sulfanilamide, had gone home against our advice and returned later with a recurrent attack, glomerular

* Furnished by the Winthrop Chemical Co.

nephritis and bronchopneumonia, another was a 70 year old male with arteriosclerotic heart disease and chronic pulmonary emphysema who died a few hours after admission, the third was a 35 year old male, with a gonococcal stricture of the urethra, a urethral fistula, extravasation of urine, cellulitis of the scrotum, pyelonephritis, hydronephrosis, uremia and syphilis, who died the day after admission. A 49 year old female with diffuse cellulitis of the leg, multiple abscesses, syphilis and toxic hepatitis was treated with one dose of sulfanilamide before the hepatitis was discovered. She died, but was not included in the treated series.

With the use of sulfanilamide, the lesions of erysipelas become dusky red and purplish within the first 12 to 24 hours and disappear completely within 4 to 10 days. The inflammatory reaction is likewise gone and the patient is subjectively better within 12 to 24 hours. No patient has had massive local desquamation following this treatment. The temperature comes down in a few days and usually by lysis. Only two of the cases had a spread of the lesion. However, there was only one spread in each instance and a very slight one.

If our experience is the general experience, sulfanilamide will become the drug of choice in the treatment of erysipelas. In cases of hepatitis or sensitivity to sulfanilamide, antitoxin may be tried on the basis that it can't do much harm and it might do some good.

An effort should be made to treat cases early, especially those cases in Groups I, III and V.

BIBLIOGRAPHY

- 1 GORDON, J. E., and YOUNG, D. C. Treatment of erysipelas with erysipelas streptococcus antitoxin, *Jr Michigan Med Soc*, 1929, **xxviii**, 353.
- 2 SYMMERS, D. Antitoxin treatment of erysipelas, results in 705 cases at Bellevue Hospital, *Jr Am Med Assoc*, 1928, **xc**, 535.
- 3 U. S. Department of Commerce, Mortality Statistics.
- 4 BIRKHAUG, K. E. Erysipelas, *Nelson's Loose Leaf Medicine*, Chap. 16, pg. 447 et seq.
- 5 BIRKHAUG, K. E. Erysipelas. Etiology and treatment with erysipelas antistreptococcic serum, *Jr Am Med Assoc*, 1926, **lxxvi**, 1411.
- 6 MCCANN, W. S. Serum treatment of erysipelas, *Jr Am Med Assoc*, 1928, **xc**, 78.
- 7 ELEY, R. C. Treatment of erysipelas in infants, report of 33 cases treated with antistreptococcus (erysipelas) serum, *Am Jr Dis Child*, 1930, **xxix**, 529.
- 8 BLACKFAN, K. Personal communication to Birkhaug, K. E., 1928.
- 9 LONG, H., and BLISS, E. A. Para-amino-benzene-sulfonamide and its derivatives, experimental and clinical observations on their use in treatment of beta-hemolytic streptococcal infection, preliminary report, *Jr Am Med Assoc*, 1937, **cxiii**, 32.

THE PROBLEM OF THE DEVELOPMENT OF HYPERSENSITIVENESS IN MAN¹

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FROM the standpoint of their development the several types of hypersensitiveness may be divided into two groups. Those in the first group are characterized by the fact that, in a given animal species, all individuals that are adequately exposed to a suitable allergen become sensitized. These types of hypersensitiveness, therefore, may be reproduced at will. In this group there are (A) the hypersensitiveness of infections, such as tuberculosis, pneumococcus infections, trichophyton infection, etc. (B) The hypersensitiveness which follows the parenteral injection of foreign substances, such as foreign blood serums (anaphylactic hypersensitiveness). (C) Contact eczema of the type which can be reproduced at will in laboratory animals or man.

In the second group the sensitivities are characterized by the fact that only a small percentage of exposed individuals become sensitized even though the exposure be very great and even repeated many times. They cannot be reproduced at will because the physiological conditions necessary for their establishment are unknown. They usually result from natural exposures—the allergen gaining entrance through the mucous membrane of the respiratory tract, the alimentary tract or through the skin. Occasionally, but not often, they follow parenteral injection, under these circumstances their occurrence is purely accidental, for previous injections of the same substance in the same individual and injections of the same substance in other individuals of the same species in many instances fail to sensitize. It is important to recognize that, in a given individual, repeated massive exposure may be entirely without effect whereas a subsequent exposure to the same substance, under external conditions which seem to be the same as before, may result in a very high degree of hypersensitiveness. Up to the present time these second types of hypersensitiveness have been observed only in man. This observation of their occurrence only in man may be the result of some peculiar human characteristic which is lacking in other animal species or, what is more probable, it may be due to our inadequate study of the other animal species. In this group there are (A) Atopic hypersensitiveness, which is characterized clinically by the conditions known as hay fever, asthma, atopic eczema, etc. (B) A condition closely related to atopic hypersensitiveness which occasionally follows the parenteral injection of such substances as insulin, pituitary extract, milk, horse serum, etc. (C) Contact eczema from such substances as nickel compounds, dyes, formalde-

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hyde, ragweed pollen oil, etc., which cannot be produced consistently experimentally

The classification of certain allergic conditions according to these criteria may seem to be somewhat difficult. For example, it is reported that monkeys and most human beings may be sensitized to poison ivy^{1,2}. Practically all normal guinea pigs may be sensitized to poison ivy³. Apparently this condition would be placed in group 1. The high degree of hypersensitivity to poison ivy often seen clinically probably cannot be reproduced at will and hence (if this is true) would be placed in group 2. Most cases of hypersensitivity to horse serum in man are relatively slight, can be reproduced at will and occur in all or nearly all injected individuals, hence they fall into group 1. The rarely observed, high degree of hypersensitivity to horse serum in man, however, falls definitely into group 2. The type of hypersensitivity found in serum sickness is placed definitely in group 1 even though serum sickness (the clinical expression of this hypersensitivity) does not occur in a very large proportion of the cases. This is probably a special condition resulting from the injection of *large* amounts of serum.

Let us consider separately the development of these two groups of hypersensitivity.

1 *Sensitivities Which May Be Induced with Regularity by Exposure to Allergens*. The hypersensitivity which occurs in the infectious diseases (the increased sensitivity, increased response to the infectious agent) is apparently an expression of an immune process. The analogy between this response to the infectious agent in disease and the response to other parenterally introduced foreign proteins of non-infectious origin was called to our attention by Von Pirquet⁴. There is indeed a remarkable similarity between serum sickness and an infectious disease. In both cases there is a foreign agent introduced into the body from without, an incubation period, general malaise, aching pains in the joints, fever, a cutaneous eruption, convalescence and recovery. In the case of an infectious disease the infectious agent may produce, in addition to non-toxic antigens, substances which are primarily toxic, the agent may localize in and injure or destroy certain organs or tissues and in other ways complicate the picture, so that recovery does not always occur. The infectious agent lives and reproduces in the body and actively manufactures antigen in the body. In serum sickness the amount of antigen is limited to that which is introduced into the body from without.

There is also an analogy in the histological appearance of the lesions of certain infectious diseases and those produced in guinea pigs by the intradermal injection of second doses of human blood serum or turtle egg or even by the first injections of these substances at the time of the "flare"⁵.

The influence of a tuberculous lesion in increasing the hypersensitivity to such substances as horse serum and egg white also suggests a relationship

between infectious diseases and hypersensitiveness to foreign substances of non-infectious origin ⁶

In many pathogenic microorganisms exotoxins have not been found. The lesions and symptoms which result from infections with these organisms may be due, partially, to the ability of these organisms to live and reproduce in the body and manufacture non-toxic antigens to which the body becomes sensitized and which are thereby rendered injurious. These antigens may be primarily no more injurious than horse serum or egg white. Imagine, for example, an organism capable of living and reproducing and manufacturing horse serum in the human body and incapable of elaborating anything else. An infection with such an organism might result in a disease resembling serum sickness which might be more prolonged or more severe because of the continued supply of the antigen produced in the body.

The most plausible explanation for the existence of the hypersensitiveness which regularly follows the injection of foreign antigenic substances into the body of man or other animal species, is the similarity in chemical composition of these antigens and those of infectious microorganisms. The body is simply unable to distinguish between the antigens of infectious microorganisms and those of certain animals and plants which are not parasites. The differences which exist between hypersensitiveness of the anaphylactic type and that of infectious diseases in general and the differences which exist among various infectious diseases may be explained on the basis of differences in chemical composition, localization, or physical state of antigens, presence and nature of toxins, varying ability of the infectious agent to live and reproduce in the body, localization in, injury to, or destruction of essential organs with resulting alteration in physiology, etc.

2 Sensitivities Which Have Not Been Induced with Regularity by Exposure to Allergens In passing to a consideration of the second types of hypersensitiveness described above, namely those types which cannot be induced at will, it is unfortunately necessary to continue to indulge in hypotheses. A consideration of these hypotheses together with some experimental evidence having a bearing upon them really constitute the chief purpose of this presentation. First we shall discuss atopic hypersensitiveness, by which we mean a type of increased reaction to a specific foreign substance characterized by the influence of an hereditary factor in its establishment, a characteristic local vascular response in a shock tissue known clinically as hay fever, asthma, atopic eczema, etc., and by the frequent but not invariable occurrence of a certain type of antibody in the blood known as atopic reagin. Other characteristics may be found in the following comparison, for which we are indebted to a great extent to Coca ⁷

ANAPHYLACTIC HYPERSENSITIVENESS AND ATOPIC HYPERSENSITIVENESS COMPARED

Similarities In both types there is a capacity to react with increased intensity to a specific foreign substance. This capacity is established by

previous contact with that substance (in atopic hypersensitiveness this latter statement is probable rather than certain) ⁷ The reaction is elicited by subsequent contact with the same substance. Antibodies are frequently present in the blood in both types. Skin tests may be obtained and shock induced by injections of the specific allergen.

Differences Anaphylactic hypersensitiveness may be induced at will in various animal species including man by parenteral injection (or other contact) with certain foreign substances. Atopic hypersensitiveness cannot be thus induced but develops under certain natural conditions which have not been identified. It is definitely known, however, as a result of statistics and of overwhelming clinical evidence, that heredity plays an important rôle in its development. Atopic hypersensitiveness has been observed, thus far, only in man. The anaphylactic type of hypersensitiveness occurs in all, or nearly all, individuals exposed to suitable antigens while the atopic type occurs in only a small percentage of those exposed.

In any one animal species the symptoms and localization of the pathology of anaphylactic shock are qualitatively the same in all individuals of that species, i.e. the shock organ is constant. In atopic hypersensitiveness, on the other hand, this localization of symptoms and pathology (shock organ) is variable, thus we have localization in the nose, bronchioles, skin, etc. (hay fever, asthma, eczema, etc.)

Atopic hypersensitiveness (in man) is usually of much higher degree than anaphylactic hypersensitiveness in man.

There are important differences in the antibodies. Anaphylactic antibodies give precipitin and complement fixation reactions, are readily transferred to such laboratory animals as rabbits and guinea pigs but not readily transferred to the human skin locally, and are more resistant to heat. Atopic antibodies (reagins), on the other hand, do not give precipitin reactions, give only an unstable complement fixation with a large prezone, are not readily transferred to laboratory animals but may easily be transferred to the human skin locally, and are less resistant to heat ⁷

In consideration of these similarities and differences there are two possible attitudes which may be taken toward atopic hypersensitiveness. The first, emphasizing the differences, is that it is something radically different from the anaphylactic type, not related in any way at all, that the similarity suggested by name (hypersensitiveness, allergy) is an unfortunate mistake. The second view, emphasizing the similarities, is that the two conditions are essentially similar and closely related, the exact relationship, being unknown, need not be specified.

For the purpose of experimentation, I made the assumption that the two conditions are related in some way and planned experiments to throw light upon this relationship, should it exist.

Two possible relationships suggested themselves. First, that atopic hypersensitiveness represents an anomalous development of the anaphylactic form dependent upon certain conditions of exposure to allergens and upon

hereditary predisposition, that it represents perhaps an over-developed or an under-developed form of the anaphylactic type. This idea has been expressed by Rackemann as a "disturbance of the immune mechanism" ⁸. In order to investigate this hypothetical disturbance Rackemann, et al compared the typhoid agglutinin response of asthmatic patients and normal persons. No significant difference, however, was found ⁹. With the same object in mind, Simon and Rackemann studied the allergic response of atopic patients and normal persons to intradermal injections of guinea pig serum, and found no clearly defined differences ¹⁰. In a further study of this problem, not previously reported, I gave repeated intradermal injections, to atopic patients, of the following substances: birch pollen, 1-50 dilution, 0.1 c.c. per injection, hen's egg white, 1-10 dilution, 0.1 c.c. per injection (and up to 0.5 c.c. undiluted egg white in 2 cases), cow's milk, undiluted, 0.1 c.c. per injection. There were twelve persons injected with each of the three substances named. The injections were given at weekly intervals for periods varying from six to ten weeks. In none of the 36 patients, however, was there evidence of the development of hypersensitiveness when skin tests were made by intradermal injection of the same substances. Hence we see that substances which are universally recognized as capable of producing a high degree of hypersensitiveness under natural conditions of exposure, when deliberately injected into atopic persons, did not produce hypersensitiveness. These findings are similar to those of Brunner ¹⁸.

This failure to produce atopic hypersensitiveness by the injection of atopens is in agreement with the work of Walzer,¹¹ Cohen,¹² Sulzberger and Vaughan,¹³ and others, who have conclusively demonstrated that, in normal persons and in atopic patients, following the introduction into the respiratory tract or into the gastrointestinal tract of such substances as fish, peanuts, ragweed pollen, silk, etc. the atopen circulates in the blood in a condition sufficiently unchanged so that it is able to preserve its specificity and produce an allergic reaction. This work indicates that the parenteral presence of atopens is of common occurrence and yet this presence of atopens does not, consistently, result in atopic hypersensitiveness, even in atopic patients. The theory that atopic hypersensitiveness is simply the result of the penetration of antigens through mucous membranes does not explain the facts and cannot be upheld.

As a possible explanation for the failure of development of atopic hypersensitiveness following the parenteral introduction of such atopens as hen's egg, cow's milk and birch pollen one might cite the work of Wells ¹⁴ on guinea pigs. In these experiments guinea pigs which had been fed egg were found to have become sensitized to egg and could be shocked by injections of egg. If, however, the feedings of egg were continued over a longer period the animals were found to have passed into a condition in which they could neither be shocked by injections of egg nor could they be further sensitized by injections of egg so that a subsequent injection would result in shock. The prolonged feeding seemed to have resulted in some such condition as

antianaphylaxis, resistance, or immunity. It might be argued that human beings do not become sensitized to hen's egg, cow's milk or birch pollen following injection of these substances because of previous continued contact with them.

In order to investigate this aspect of the problem I gave repeated intradermal injections to atopic patients of the following substances: mare's milk, undiluted, 0.1 c.c. per injection to 12 patients; turtle's egg, 1-10 dilution, 0.1 c.c. per injection to 12 persons. In none of the 24 persons was there evidence of the development of hypersensitiveness when skin tests were made by intradermal injection of the same substances. Mare's milk and turtle's egg are biologically similar respectively to cow's milk and hen's egg and in the case of turtle's egg the immunological specificity was investigated and found to be distinct from hen's egg, as shown by the following evidence: 3 guinea pigs sensitized to turtle's egg did not react to hen's egg, and two patients atopically sensitive to hen's egg, who gave large skin tests to hen's egg, gave no skin reaction at all to turtle's egg. Hence the idea of previous contact with the allergens of turtle's egg in the form of common allergens present in hen's egg cannot be upheld. This investigation, therefore, would indicate that the objection based on Wells' work is not valid, namely that previous continued contact with hen's egg does not constitute an explanation for the failure of development of atopic hypersensitiveness following parenteral injection of this allergen.

In contrast with this failure to produce atopic hypersensitiveness in man by injection of these allergens we have the ease with which the anaphylactic type may be produced in man by the injection of guinea pig serum.⁹ This hypersensitiveness to guinea pig serum passes through the same stages as that observed in the guinea pig and undoubtedly represents the analogous phenomenon in man. A quantity of guinea pig serum less than 0.001 c.c. is sufficient to sensitize a man in some cases and 0.01 c.c. is sufficient in practically any case.

A second possible relationship between hypersensitiveness of the anaphylactic and atopic types is suggested by the work of Dienes with tuberculous guinea pigs in which it was shown that the injection of an antigen into a tuberculous lesion in a guinea pig results in the development of a much higher degree of hypersensitiveness than the injection of the same antigen into a normal animal. Since one of the characteristics of atopic hypersensitiveness is that it is often of much higher degree than anaphylactic hypersensitiveness in man, as measured by skin tests, one might suspect that atopic hypersensitiveness represents hypersensitiveness of the anaphylactic type which has been modified by infectious disease in an hereditarily predisposed individual. To be more specific one might form the hypothesis that a person with hereditary predisposition would develop ragweed pollen asthma provided he had an attack of acute bronchitis during the ragweed season, another such predisposed person would acquire grass hay fever because of an acute infectious rhinitis during the grass pollen season, and a third such per-

son might become sensitized to egg because egg happened to be the food taken in large amounts during an attack of enteritis

In order to investigate this hypothesis patients with infectious diseases were exposed to two allergens. The allergens chosen were guinea pig serum and turtle egg, the former because it is a good antigen for man, the latter because it is a poor antigen for man, and both were selected because they are substances with which a later contact would be very unlikely. All patients were exposed to both substances in 1 to 10 dilution. The usual method of application was to apply to the nasal mucous membrane a cotton applicator saturated with the solutions, a method previously found to be effective in producing hypersensitiveness to guinea pig serum¹⁰. In addition many patients were given applications to the throat by swabbing with applicators saturated with the solutions. In several cases the solutions were also injected intradermally in quantities of 0.1 cc to each patient. In the entire series there were 18 patients. Of these, six had diphtheria, five measles, two scarlet fever, two streptococcic sore throat, one mumps, and two chicken pox. Approximately three weeks after treatment with turtle egg and guinea pig serum skin tests were made in all cases by intradermal injection of these substances in dilutions of 1-10 and 1-100. The results were the same in all cases, that is, all gave positive skin tests to guinea pig serum and all negative tests to turtle egg. All patients reacted to these allergens just as one might expect them to react had they not been sick with an infectious disease, with the exception that in a few cases the hypersensitiveness appeared to be somewhat weaker than one might expect in a healthy subject. As controls there were a series of more than 100 persons sensitized to guinea pig serum (by intradermal injection and by application of the serum to the nasal mucous membrane) and the twelve patients previously discussed who were injected with turtle egg.

Apparently the infectious disease was without influence on the development of the hypersensitiveness except perhaps to weaken it in several cases. There was no evidence of an increased sensitivity greater than in the controls in any case. The allergen was introduced as early as possible in the course of the disease but in every instance the disease was clinically well developed when the exposure was made. This may constitute an objection and explain the negative results, since, according to the experience of Dienes, the antigen must be injected into the tuberculous lesion early in the course of the infection. Since the patients were chosen at random rather than selected on the basis of atopic history, the presence of an hereditary predisposition in any is not guaranteed. From the evidence available, however, it is apparent that the infectious diseases studied did not increase the degree of hypersensitiveness and certainly did not make it possible to produce atopic hypersensitiveness at will by exposure to allergens.

It must be concluded, therefore, that these experiments planned to investigate a possible relationship between the atopic and the anaphylactic types of hypersensitiveness have failed to disclose such a relationship.

The hypersensitiveness which occasionally occurs following the injection of such substances as insulin,¹⁵ pituitary extracts,¹⁶ liver extract,²⁰ etc is sometimes of very high degree, may be accompanied by the presence of antibodies of the atopic type (reagins) and occurs in only a small percentage of exposed persons. The presence of an hereditary influence in its establishment is probable. Hence it resembles atopic hypersensitiveness. It often differs, however, in one important respect, namely in the absence of a typical atopic clinical syndrome such as hay fever, asthma or atopic eczema. This absence of an atopic syndrome may be due to the fact that exposure to biological products such as insulin and pituitary extracts is usually by parenteral injection rather than by inhalation or ingestion. This type of hypersensitiveness resembles the atopic type more closely than any other recognized variety and may fundamentally be identical with the atopic type, modified in its manifestations and in its mode of establishment only by the route of exposure to the allergen. The fundamental importance of the predisposed shock organ in atopy should constantly be held in mind, however, and with the evidence at present available a definite decision is not justified on this point.

Concerning hypersensitiveness to drugs of several clinical forms such as a number of clinical varieties of skin eruptions, asthma, purpura, etc., the evidence suggests that the true allergen is a combination of the drug with body proteins. Hence, with the exception of the origin of the allergen, there is no fundamental reason for regarding this type of hypersensitiveness as differing from those due to the usual inhalants and foods. It may be atopic in some cases and non-atopic in others.

In the hypersensitiveness seen in contact eczema the epidermis plays an important part. The reactions are always of a delayed type for the obvious reason that vascular changes cannot occur in the epidermis, since it is not a vascular tissue. Concerning the establishment of this type of hypersensitiveness we know very little. Heredity is not known to be a factor, but this aspect of the problem has not been carefully studied. With most of the allergens of contact eczema, such as nickel salts, quinine, azo dyes, mercury compounds, formaldehyde, etc. only a small percentage of exposed persons become sensitized.

In the case of poison ivy, however, Straus reports that it is possible to sensitize a majority of human infants and monkeys^{1,2}. Practically all normal guinea pigs may be sensitized to poison ivy³. Spain reports that about two-thirds of apparently normal human adults are sensitive to poison ivy in varying degree, the percentage reacting to any given concentration of poison ivy extract being proportional to the logarithm of the concentration of the test extract.¹⁷

In consideration of these data it appears reasonable to assume that there are two types of contact eczema, analogous respectively, from the developmental standpoint, to atopic and anaphylactic hypersensitiveness. The type usually seen clinically is analogous developmentally to atopy and cannot be

reproduced at will experimentally. The type which can be produced at will in guinea pigs, monkeys or in human infants by exposure to poison ivy is analogous to anaphylactic hypersensitiveness. This latter type, in the guinea pig and monkey (and probably also in artificially sensitized human infants) is very much weaker than the usual clinical case of ivy poisoning. It is also well to remember, in dealing with a substance such as poison ivy, that primary irritation may be confused with allergic reaction. Poison ivy extract is definitely irritating to the skin of a guinea pig even before sensitization has developed. Hence it is worth inquiring, in the case of the work reported by Spain, referred to above,¹⁷ whether those persons who reacted to the very strong extracts did so as a result of allergic sensitivity or as a result of the primary irritation of the extract used in the test.

To illustrate this concept more specifically, poison ivy sensitivity produced experimentally in human beings, monkeys and guinea pigs is analogous (developmentally) to horse serum sensitivity produced experimentally in human beings and in guinea pigs, whereas clinical ivy sensitivity in man is analogous to the rarely encountered, high degree of sensitivity to horse serum in man. It is true that *occasionally* a very high degree of sensitivity to horse serum and to poison ivy may be produced "experimentally."¹⁹ The significant fact is that neither can be *consistently* produced experimentally. (My technician and I have repeatedly spilled strong poison ivy extracts on our hands without having become sensitized, and I have deliberately tried to sensitize myself without success.)

In considering once more the general problem of the development of hypersensitiveness in the second group of sensitivities, namely those which cannot be produced consistently experimentally, the present need is not to attempt to decide what relationship, if any, exists between these two groups but rather to study the sensitivities themselves more thoroughly in order that we may learn the facts which will enable us to decide what relationship, if any, exists between them.

In studying these sensitivities which cannot be produced experimentally there are several important and fundamental problems to be investigated. Among the more important of these there are two which would seem to deserve special consideration. First, what factors determine that some individuals become sensitized whereas others in the same environment with apparently the same exposures are exempt? Second, among those who become sensitized what determines the specific substances to which hypersensitiveness develops? With regard to the first problem we need to investigate the physiological conditions under which it is possible for these types of hypersensitiveness to develop. The influence of heredity in atopy should be investigated further and should be regarded as a challenge to determine its physiologic mode of action. The influence of heredity does not remove this problem from physiologic investigation. The influence of heredity in the etiology of diabetes mellitus, for example, is generally recognized and yet the study of diabetes from a physiologic standpoint has been of great

practical value in the understanding and treatment of the disease. The possibility of other factors in addition to exposure to atopens and heredity must also be investigated. The clinical evidence suggests that, in the case of atopy, patients are in a condition predisposed to the development of hypersensitiveness for relatively brief intervals rather than continuously throughout their lives or continuously after a certain period of their lives. In support of this concept we have the following evidence: 1. Injection of such substances as pollen extracts, insulin, pituitary extracts, liver extract, horse serum, guinea pig serum, etc. into atopic patients very rarely if ever results in the production of atopic hypersensitiveness. 2. In the rare instances in which the injection of such substances results in a high degree of hypersensitiveness with reagins (the atopic nature of which has been questioned, chiefly on the basis of the absence of an atopic syndrome) previous injections of the same substance and subsequent injections of other atopens frequently are without effect in producing hypersensitiveness. 3. Many persons living in the ragweed pollen area have inhaled this pollen every fall for many years without having become sensitized to it, while during this same period of their lives they have become sensitized to other pollens present in the air at some other season, such as timothy, oak, birch, etc.

The second problem to which reference was made, namely the determination of the specific allergens to which sensitization develops, may be closely related to this first problem. Two possibilities suggest themselves: (1) That the capacity to become sensitized is specifically directed toward some particular substance and not toward other substances.⁷ According to this interesting theory one man becomes sensitized to ragweed pollen because he has been born with the inherited capacity to become sensitized to this substance and he does not become sensitized to grass pollens because of the absence of the hereditary determiners for sensitization to grass pollens (or absence of exposure to grass pollens). (2) Another, and perhaps more plausible hypothesis, would be one which supposes a nonspecific predisposition to the development of hypersensitiveness, present for comparatively short intervals of time, the specific allergen to which hypersensitiveness develops being determined by the following circumstances: (A) Exposure to that particular allergen, (B) the coincidence of this exposure with the period of predisposition, (C) some accidental occurrence at the time of exposure (such as an infectious disease, evidence for which was not found in the experiments described above). In support of this hypothesis one may cite the following clinical evidence, which is in the nature of a clinical impression rather than statistical evidence: (1) Patients sensitive to wheat are usually sensitive to several of the separate protein constituents of wheat rather than to only one of these constituents. This would indicate that the simultaneous exposure to several substances, all of which are good allergens, results in hypersensitiveness to each of the several substances. This concept is also in agreement with the well recognized fact that allergic patients are usually sensitive to more than one substance. (2) Patients sensitive to tree

pollens are often sensitive to two or more tree pollens which are in the air at the same time interval even though these trees are of unrelated species and probably do not contain common allergens. A study of sensitivity to the individual components of mixtures of allergens and a statistical study of sensitivity to pollens in the air at the same time would be of value in contributing to the solution of this problem.

REFERENCES

- 1 STRAUS, H. W. Artificial sensitization of infants to poison ivy, *Jr Allergy*, 1931, ii, 137
- 2 STRAUS, H. W. Studies in experimental hypersensitiveness in the rhesus monkey, 1 Active sensitization with poison ivy, *Jr Immunol*, 1937, xxxii, 241
- 3 SIMON, F. A., SIMON, M. G., RACKEMANN, F. M., and DIENES, L. The sensitization of guinea pigs to poison ivy, *Jr Immunol*, 1934, xxvii, 113
- 4 VON PIRQUET, C., and SCHICK, B. Zur Theorie der Incubationzeit, Vorläufige Mitteilung, *Wien klin Wchnschr*, 1903, xvi, 758
- 5 DIENES, L., and SIMON, F. A. The flaring up of injection sites in allergic guinea pigs, *Jr Immunol*, 1935, xxviii, 321
- 6 DIENES, L., and SCHOENHEIT, E. W. The reproduction of tuberculin hypersensitiveness in guinea pigs with various protein substances, *Am Rev Tuberc*, 1929, xx, 92
- 7 COCA, A. F., WALZFR, M., and THOMMEN, A. A. Asthma and hay fever in theory and practice, *Chas C Thomas*, pgs 38 to 57
- 8 RACKEMANN, F. M. The nature of allergy, *Trans Am Clin and Climat Assoc*, 1930, xli, 72
- 9 RACKEMANN, F. M., SIMON, F. A., SIMON, M. G., and SCULLY, M. A. Further observations on the nature of allergy, *Jr Allergy*, 1933, iv, 498
- 10 SIMON, F. A., and RACKEMANN, F. M. The development of hypersensitiveness in man, *Jr Allergy*, 1934, v, 439
- 11 WALZER, M. A direct method of demonstrating the absorption of incompletely digested proteins in normal human beings, *Jr Immunol*, 1926, xi, 249
- 12 COHEN, M. B., ECKFR, E. E., and RUDOLPH, J. A. Disappearance time of circulating ragweed pollen material after absorption from nose and throat, *Jr Allergy*, 1930, i, 529
- 13 SULZBERGER, M. B., and VAUGHAN, W. T. Experiments in silk sensitivity and the inhalation of allergen in atopic dermatitis, *Jr Allergy*, 1934, v, 554
- 14 WEILS, H. G. The present status of the problems of anaphylaxis, *Phys Rev*, 1921, i, 44
- 15 TUFT, L. Insulin hypersensitiveness, immunologic considerations and case reports, *Am Jr Med Sci*, 1928, cxlvi, 707
- 16 SIMON, F. A., and RYDER, C. F. Hypersensitiveness to pituitary extracts, *Jr Am Med Assoc*, 1936, cvi, 512
- 17 SPAIN, W. C., NEWELL, J. M., and MFLKFR, M. G. The percentage of persons susceptible to poison ivy and poison oak, *Jr Allergy*, 1934, v, 571
- 18 BRUNNFR, M. Active sensitization in human beings, *Jr Allergy*, 1932, iii, 521
- 19 FIFID, H., and SULZBERGER, M. B. Experiments in poison ivy sensitivity, *Jr Allergy*, 1936, vii, 139
- 20 CRIFF, L. H. Personal communication

ELECTROPYREXIA, TECHNIC OF APPLICATION AND THERAPEUTIC INDICATIONS *

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THE technic of artificial fever has changed considerably during the last three years. The field of usefulness of artificially induced fever has widened considerably and in spite of over-enthusiasm of some, and the tendency to use it without any regard to cause and effect by others, it is now recognized to be quite useful in the field of therapeutics. Paralleling this increase in usefulness, several different kinds of apparatus for producing fever have been developed, the use of which has led to much confusion.

The first problem that arises when one desires to employ artificial fever as a therapeutic procedure is: What method should be used? From the literature, this question is not readily answered for several reasons. One reason is, that it is not difficult to convince oneself that the apparatus one is using and accustomed to is the ideal, and that any deviation from such an apparatus and method is radically wrong. The second reason is, that a well-trained personnel is of vital importance in administering artificial fever, and that such a personnel can use successfully any of the well-recognized methods. Yet it is believed that such a group should not labor under a handicap if real differences exist, therefore, a careful consideration of the method to be employed is in order.

At present there are two distinct methods used for producing artificial fever in man. *First*, by means of an externally heated environment. Examples are the air-conditioned Ketting hypertherm, infra-red radiation, such as the electric light cabinets, and hot water baths. *Second*, the production of heat in the body by means of high frequency currents such as diathermy, high frequency electric fields, or electromagnetic induction.

The use of hot water is too dangerous a procedure to be given any consideration. Mehrtens and Poupourit¹ who introduced the hot water bath method were unable to maintain the temperature of their patients for more than a few hours. That temperature can be maintained by this method was first demonstrated by Merriman and Osborne². These authors state, however, that this is the most dangerous method so far devised, and advise against its use.

We first employed the high frequency current as introduced by Neymann and Osborne³. Since then we have tried every method advocated up to the present time in an endeavor to find the best method available. Our experiences have led us to the conclusion that the use of high frequency current

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for producing artificial fever has a much wider margin of safety for the patient than external heating methods, and is far more comfortable. These observations were largely empiric in nature at first but gradually physiological investigations are tending to substantiate the bedside observations. Neymann and Osborne¹ have shown that when external heat was used the natural heat gradient of the body was reversed, while this was not true when high frequency currents were used to produce internal heating (Figure 1). They also showed that there is a greater water loss by way of the skin (table 1), when internal heat is used.

TABLE I

Effect of External and Internal Heat on Perspiration Output Less Danger of Heat Stroke When the Patient Is Perspiring Freely *

Patient Number	Type of Treatment	Date	Temperature Above 103.5° F	Temperature Above 105.8° F	Water Intake	Calculated Perspiration Output
1	Blanket	Mar 16	8 hr	4 hr	2,290 c c	4,340 gm
1	Diathermia	Apr 3	8 hr	4 hr	2,575 c c	5,048 gm
2	Blanket	Mar 23	8 hr	4 hr	2,350 c c	3,491 gm
2	Diathermia	Apr 3	8 hr	3½ hr	3,375 c c	4,683 gm
2	Radiothermia	Apr 6	10½ hr	4 hr	3,420 c c	4,216 gm
3	Blanket	Nov 28	8 hr	2¼ hr	3,250 c c	3,453 gm
3	Diathermia	Dec 8	8 hr	2¼ hr	5,200 c c	6,141 gm
3	Radiothermia	Dec 18	7½ hr	2½ hr	4,110 c c	3,960 gm

* NEYMANN, C A, and OSBORNE, S L. *Am Jr Syph*, January, 1934

Gibson, Kopp and Evans² reported at the International Fever Conference 1937, their studies in plasma volume. They stated that with the Kettering hypertherm air-conditioned cabinet, reduction in blood volume was extreme, and occurred early in the course of fever reduction, with the result that a severe degree of tissue dehydration takes place by the time therapeutically desired temperatures were obtained. With diathermy, a considerable reduction in plasma volume did not take place until high temperatures had been reached. These investigators state that, in their opinion, the degree of dehydration and danger of serious circulatory disturbance is considerable during fever induced by the Kettering hypertherm, even when fluids are liberally given by mouth. Our observations have confirmed their opinion. Gibson, Kopp and Evans also showed that the degree of alkalosis was most marked in patients treated by externally applied heat. Moreover, we have found that the pulse rate was usually lower by approximately 20 beats per minute when internal heat was used as opposed to the findings with external heat (figure 2). Again, the high environmental temperature to which the patient is exposed throughout the treatment when external heat is

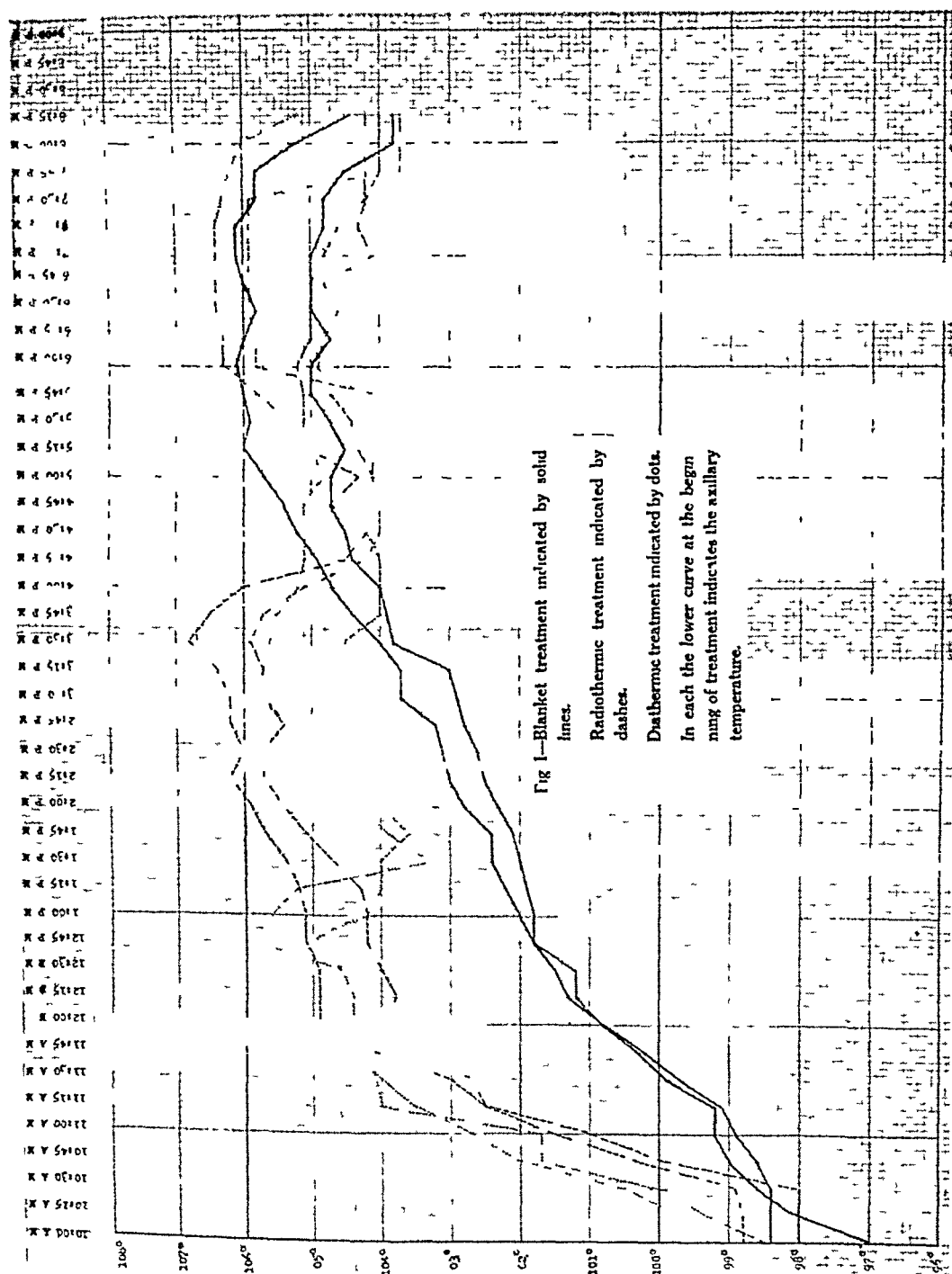


FIG 1 Comparison of external and internal heating of the body. External heat reverses the natural heat gradient (Neymann and Osborne, Physiology of hyperpyrexia, Am J Syphilis and Neurology)

used, apparently predisposes more readily to heat stroke and circulatory collapse. Delirium seems to be more frequent.

Regardless of the method used, it is imperative that careful attention be given to prevent heat loss from the patient if a temperature is to be maintained for a number of hours. Successful temperature maintenance depends on this.

In this respect marked progress has been made. The methods first advocated seem very crude today. The use of a treatment bag (which is

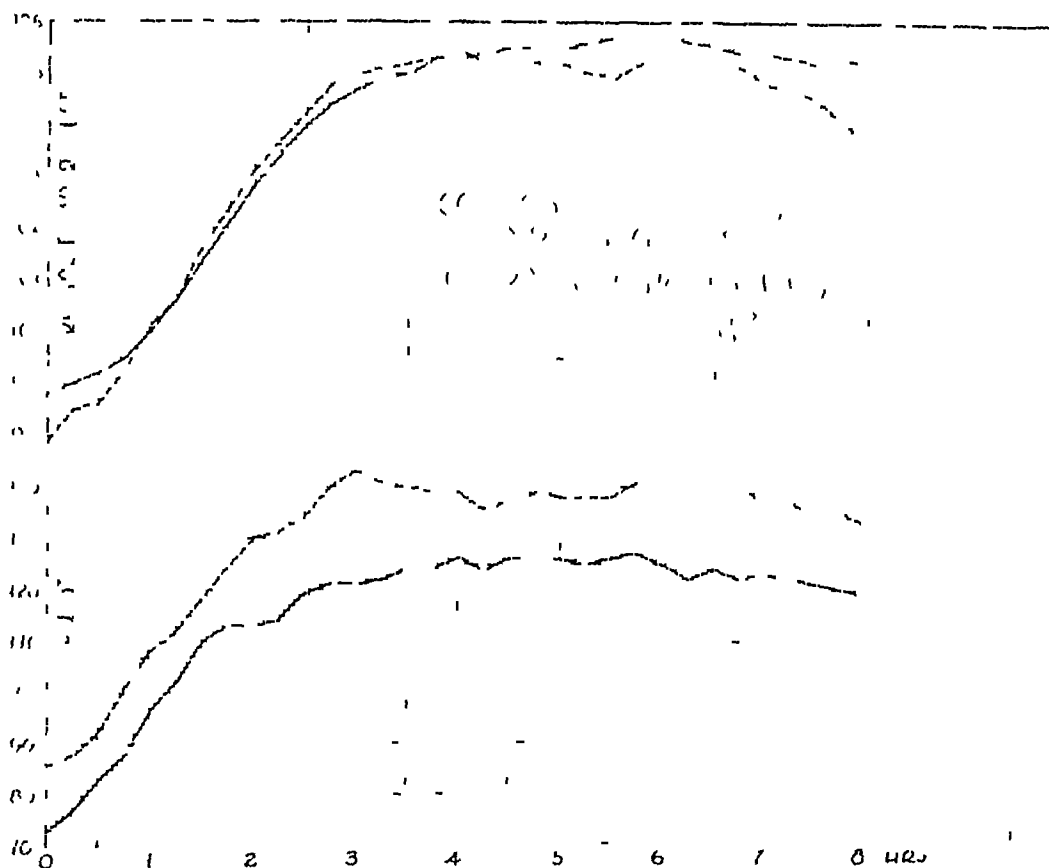


FIG. 2 Effect of external and internal heat on pulse rate

essentially a well-insulated sleeping blanket) was a distinct step forward, but this has certain disadvantages, such as the restriction of the patient's movements and the weight of the bag upon the patient, particularly upon the feet. It is not easy to keep the bag clean. These disadvantages have been successfully eliminated by the use of some form of cabinet to retard heat loss and at the same time use the high frequency current to raise the body temperature to the desired therapeutic level. A wooden cabinet with air conditioned features has been used, but such a cabinet has the disadvantage of warping and of being quite heavy and bulky. Nevertheless it was a step in the right direction. Recently a much cheaper and more durable cabinet

has been devised. It is so light and portable that it may be moved to any room in the hospital, and is constructed almost entirely of polished metal (figures 3, 4, 5). We believe that such a cabinet will largely supersede the "zipper treatment bag."

We shall first describe the "zipper bag treatment technic." Our method is as follows. The bag is fully opened and one-half of the bag placed on the bed so that when the patient lies down, the middle of the neck is level with the top of the bag. A full-sized rubber sheet is laid over this to prevent heat loss through the bag and to keep the bag as dry and clean as possible. Next, a bath blanket, or a light woolen blanket folded like a shawl, is placed over the rubber sheet at the upper end with the apex of the shawl directed toward the foot of the bed. This blanket serves the purpose of preventing heat loss from the region of the neck when the zipper bag is closed. Next, a special terry cloth is laid over the entire rubber sheet and shawl-shaped blanket. The cloth must be so placed that the open side, when the cloth is folded over to cover the patient, will be towards the special opening provided in the bag to obtain access to the patient once the bag is closed. After the patient is covered with the terry cloth, it is quite closely approximated around the neck and shoulder, and held in place with a safety-pin. Next, the shawl-shaped blanket is brought around and fitted snugly to the neck to prevent the escape of heat from the bag. The zipper bag is now closed and the 12-foot cable, to be connected later with the electromagnetic generator, is formed into a single elliptical loop about four feet long and one foot wide. It extends approximately from the shoulder level to the middle of the lower leg (figure 6). Occasionally it is necessary to fold the blanket into two thicknesses and place it under the coil in the region of the lower legs, if the patient complains of too much heat in that region. A full length rubber sheet is placed over the coil and two additional blankets are added when necessary. The coil is now connected to the inductotherm and the current turned on.

The *electromagnetic cabinet technic* is very simple. The cabinet is opened (figure 4) and a large terry cloth is folded and so placed over the special mattress that the patient will lie on the lower half and be covered with the upper half. The cabinet is then closed, the neck outlet is closed with a pillow, and the heater and humidifying apparatus is turned on to preheat the cabinet to 110° F. This is to prevent the transfer of heat from the patient whose temperature is approximately 98.6° F to the air of the cabinet. When 110° F is reached, the patient is placed between the layers of terry cloth (care being taken to well insulate around the neck) the cabinet closed and the electromagnetic generator turned on (figure 5). When the patient's rectal temperature reaches the desired level, the electromagnetic current is turned off and the required temperature level is maintained by regulation of the cabinet temperature which is accomplished by a variable resistance switch. The ideal cabinet temperature is the lowest that will retain the patient's temperature level. This cabinet temperature should not exceed 110° F and is usually kept between 100° to 105° F. A special opening is provided for taking care of the patient's needs, such as the bed pan, and for rectal temperature readings or other necessary observations. The heated air is circulated and humidified to between 90 and 95 per cent, although humidification is not automatically controlled.

Before prescribing fever, the physician should determine whether it is of therapeutic value for the disease under consideration. Lack of confidence on his part is usually unconsciously transferred to the patient. The treatment produces discomfort and does so because the patient is hot and his body temperature above its normal range. The degree of discomfort varies with the patient and the method used to raise the temperature. Patients should be prepared for the discomfort, but

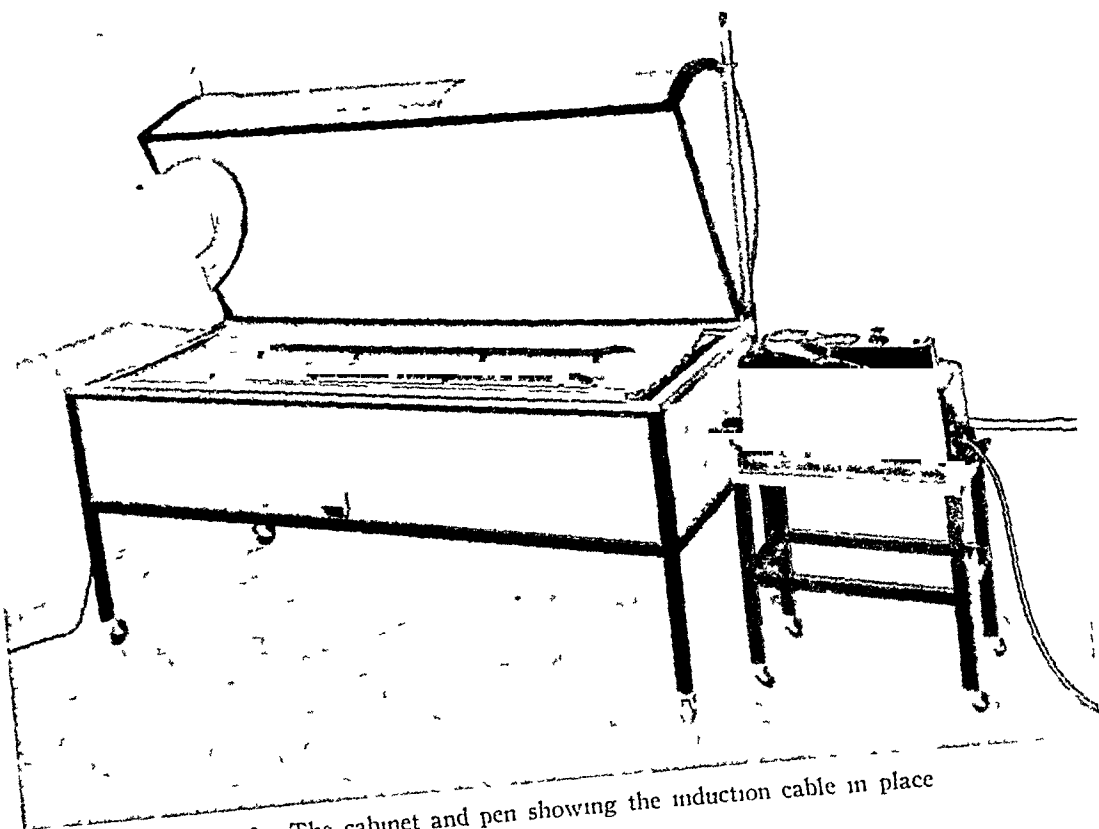


FIG 3 The cabinet and pen showing the induction cable in place

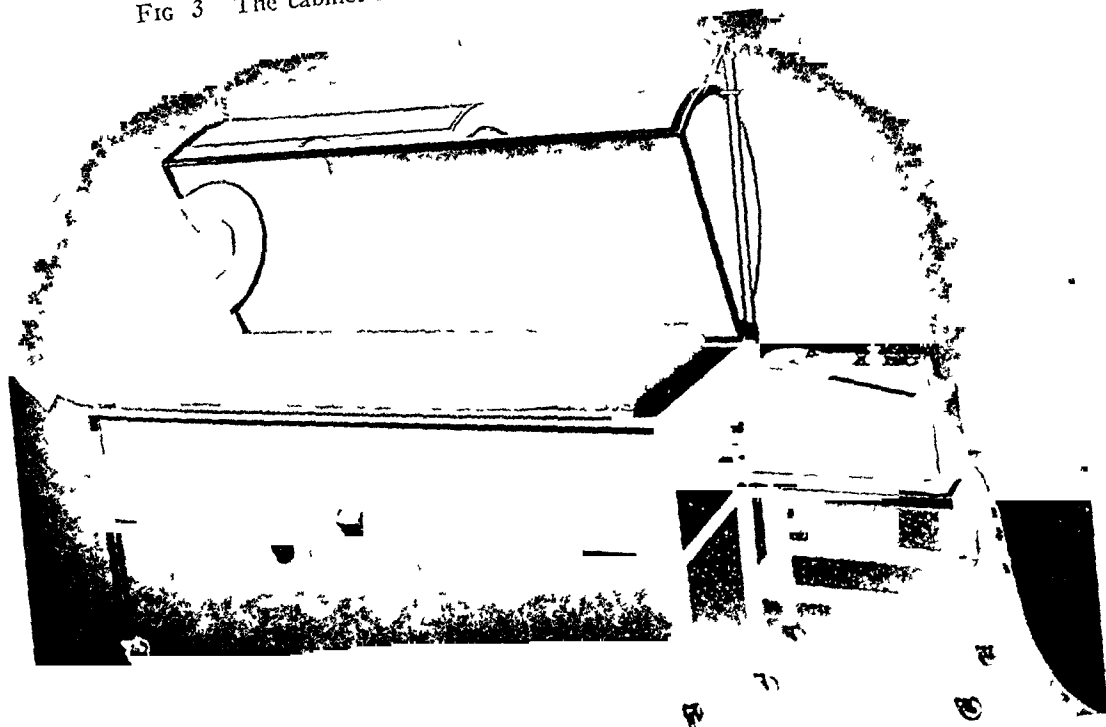


FIG 4 The cabinet open and ready for the patient The terry cloth to cover and wrap the patient in has been removed to show the airtex mattress covering the induction coil

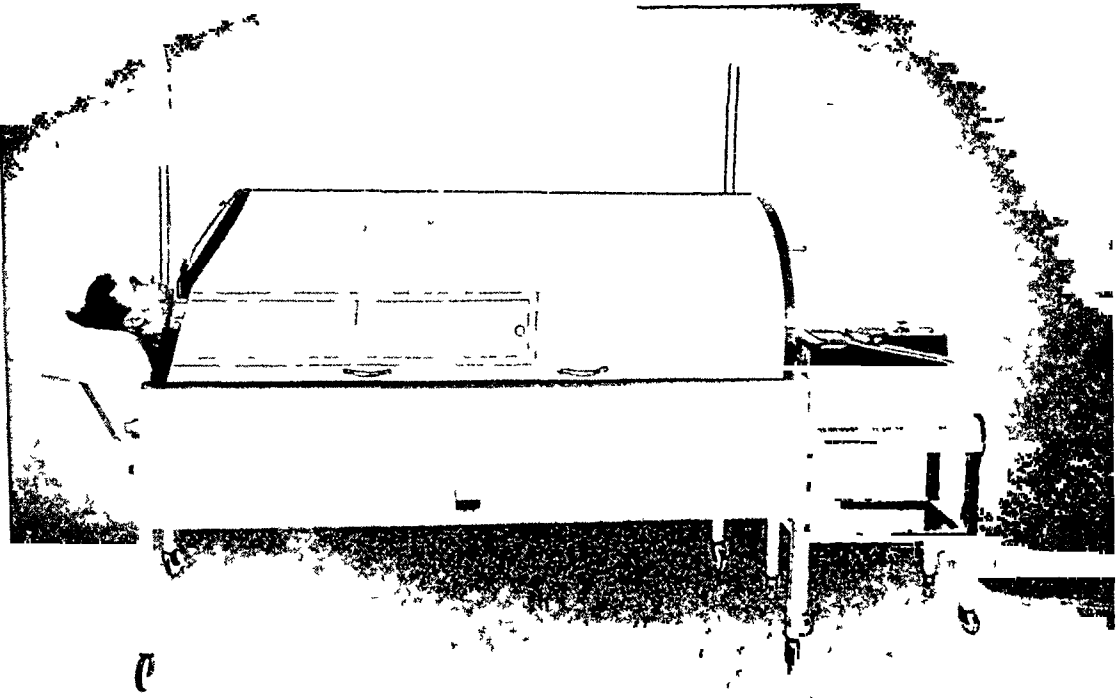


FIG 5 The patient ready for treatment



FIG 6 Patient in zipper treatment bag with inductance cable in position ready for the electromagnetic current to be turned on Note resistance thermometer (rectal) entering at small zipper pocket

it should not be emphasized to the extent that the patient becomes unduly apprehensive. The patient or relatives should be told that such treatment is not without hazard, but when properly used the dangers are remote. The proper psychotherapy will do much to allay the patient's natural apprehension.

The contra-indications to this form of therapy must be considered.

Before accepting a patient for fever therapy he should be given a thorough physical examination which should also include an electrocardiographic and a routine clinical blood examination. If any doubt exists relative to the fasting blood sugar level, it is advisable to perform a glucose tolerance test in order to determine the possibility of impending hypoglycemic shock.

The patient should be given an enema the evening preceding the treatment, and the breakfast on the morning of treatment should be light, consisting largely of fluid foods or foods evacuated from the stomach within two hours. The use of drugs which inhibit perspiration, such as hyoscine, should be discontinued several days prior to the exhibition of fever therapy, and such drugs should never be given during treatment.

Some workers advise the use of sedatives before beginning the treatment. Schmidt⁶ gives 15 to 30 grains of pentabromides in the form of the elixir, just before the treatment is started. He repeats this dose 30 minutes later. If the patient is still restless when the desired temperature level is reached, he gives pantapone, $\frac{1}{2}$ gr hypodermically. We do not use sedatives at the beginning of the treatment and only when absolutely necessary during treatment. We use from $\frac{1}{8}$ to $\frac{1}{4}$ of a grain of morphine sulphate, and give it when the current is turned off. We endeavor in so far as possible not to use hypnotics. This matter is, however, an individual one, and nearly every fever therapist has his own particular views on the subject. However, drugs which tend to inhibit secretions, or produce peripheral vasodilation or excessive sweating, should not be used.

Once treatment has started, the nurse should be in constant attendance, and a physician within call. Her tact and understanding will do much to alleviate the patient's discomfort. The patient's face should be kept free of perspiration, and this is best done with a wet hand-towel. She should record the pulse, respiration, and rectal temperature every 15 minutes. The rectal temperature is taken by an ordinary clinical thermometer when electromagnetic induction is used, until the current is discontinued, and then for the remainder of the treatment an indicating resistance thermometer, as illustrated, is used. We feel that this instrument is invaluable because the patient's temperature may be kept under observation continuously and can be very accurately controlled at all times. The current is discontinued usually at approximately from one to two degrees Fahrenheit below the maximum temperature that is required. This is necessary because the patient's temperature will continue to rise from one to two degrees after the current is turned off. Usually the extent of the secondary rise can be gauged by the temperature increment with each 15 minute interval. The secondary rise is usually proportional to this increment so that with an increment of one degree or more the secondary rise will be much greater than when the 15 minute increments are below one degree Fahrenheit. The nurse should be instructed to keep the temperature within a certain range and for a given period of time. If the temperature consistently drops, it may be due to heat loss from some part of the insulation around the patient, particularly around the region of the neck. If the temperature has a tendency to rise, it frequently can be checked by applying a folded bath towel saturated with ice water and placed over the head and face in the form of a compress. Such a simple procedure will often maintain the desired temperature within a range of plus or minus 0.1° F. We also employ an electric fan to direct a current of air over the patient's head and face for short intervals, if the cold compress is not adequate. Occasionally it is necessary to open the side pocket of the treatment bag or the side panel of the cabinet. The nurse must, however, be familiar with the procedure necessary to cool a patient, when required.

During treatment, patients perspire freely, with a consequent water and chloride loss. To counteract any ill effects, we give patients a 0.6 per cent NaCl solution to drink—that is, 6 grams NaCl to one liter of water. This concentration is not particularly unpalatable. Three to four liters of fluid are usually taken in, during a treatment. If, however, a patient expresses a desire to have any other beverage, we usually give it, if available. With children we use fruit juices quite freely with some form of sugar added. It is well to administer the fluids frequently in small quantities to avoid gastric distention and nausea. Iced beverages should be avoided.

Whenever a bed pan or urinal is needed it should be preheated and given to the patient through the opening provided for that purpose, care being used to lose as little heat as possible through the opening. The electric current must always be switched off during the use of the bedpan in order to avoid the possibility of burns from the metal. A vague aching distress in the lower abdomen may be due to a distended urinary bladder, and voiding of urine may give prompt relief.

Friends or relatives should not be permitted to visit the patient during the treatment, since they often disturb and worry the patient. The room should be warm, well ventilated, and darkened so as to make conditions as conducive to sleep as possible. Noise and confusion should be carefully avoided. The physician referring the case for fever therapy should visit the patient after the fever has been induced as this will often lend confidence and assurance to the patient. The physician under whose supervision the treatment is being given should visit the room frequently and show his interest in the outcome of the treatment. He should always be readily accessible during and for an hour after the treatment.

The nurse should be thoroughly familiar with all the warning signs which indicate that the temperature should be lowered or discontinued. Two potential dangers are omnipresent: one is a disturbance of the heat regulatory mechanism, resulting in heat stroke. This danger is intensified when high external temperatures surround the body. (Drugs which reduce perspiration excessively should not be used.) The other danger is circulatory collapse due to an unusual peripheral vasodilation, which results in an insufficient quantity of blood reaching the right side of the heart. For this reason no drug should be used as a hypnotic that has a tendency to produce engorgement of the peripheral blood vessels. The warning signals are the appearance of circumorbital pallor, marked irregularity of respiration, sharp drop, rise, or irregularity in rhythm and amplitude of the pulse rate. A marked diminution in perspiration is a major danger demanding continuous and careful attention, in such an instance it may be necessary to lower the temperature or even discontinue the treatment to safeguard the patient. The appearance of an almost imperceptible twitching of the muscles around the lips is an absolute sign contraindicating the continuance of the treatment, especially when treating chorea minor. When it becomes necessary to terminate treatment abruptly, covers are all removed from the patient, except for a light sheet across the pelvis, and the temperature is reduced as rapidly as possible by means of an electric fan directed across the body, and of ice cold applications restricted largely to the head, face, neck, and upper chest. A very effective means of stimulating respiration when necessary is to place one's hands in ice cold water and forcibly shake water from them on the patient's chest. When the temperature has fallen to a level of approximately 102° F these radical procedures should be discontinued. The patient is then covered with a light blanket or sheet, and if the patient at any time complains of chilliness, he should be adequately covered. Probably the best method to combat circulatory collapse is to administer saline and glucose solution intravenously. Caffeine sodium benzoate is, we believe, the best heart stimulant to be used in these cases. In case of impending respiratory failure, the ideal procedure is to administer by a face mask, a mixture of 95 per cent oxygen and 5 per cent carbon dioxide as a respiratory stimulant.

When it is time to terminate the fever at the end of a successful treatment, all covers are removed from the patient. The patient is asked to inform the nurse as soon as he feels the least sign of chilliness, then the nurse covers the patient with a light covering such as a sheet or blanket. When the rectal temperature drops to 100° F, which usually requires from 30 minutes to two hours, the patient is given a tepid sponge bath, an alcohol rub, and returned to his room. Instructions are given to keep the patient in bed until the following morning, he being allowed any food he might desire. His temperature is taken hourly during the night to be sure that no secondary rise occurs.

Electropyrrexia, since its introduction, has been used in the treatment of many conditions. Krusen²¹ reported its use in no less than 50 different conditions during 1935. We shall confine discussion to those diseases in which electropyrrexia appears to have decided merit.

GENERAL PARESIS

Dementia paralytica was the disease first treated by electropyrrexia, and the literature now contains the reports of 809 patients who have been treated here and abroad. Various authors have reported different remission rates. This, it would seem, indicates the necessity of following a definite standardized technic.

First, the selection of patients is important. Grandiose and expansive types with sudden onset have an excellent chance of reaching a perfect mental adjustment. Slowly dementing and depressed parietic patients are to be looked upon as more serious risks, and deteriorated parietic patients who have become demented to such an extent that they lead a purely vegetative existence, are hopeless, and should not be treated.

Second, the fever in the treatment of dementia paralytica should be maintained at a given height for a definite period of time. Bessemans⁷ has determined the thermal death time of *treponema pallidum* both in vitro and vivo. As a result of his researches a fever above 103.5° F for at least six hours, with an additional two hours at 105.8° F, has been used. Thus the fever is maintained for a period of at least eight hours. The two hours of high temperature is permitted at any point during the treatment, but is usually best tolerated at about the fourth and fifth hours. Treatments are given twice weekly, and usually 20 treatments constitute a course.

The serologic changes do not correspond to the amount of clinical improvement. A decrease in the number of cells usually occurs after a series of treatments. The Pandy reaction occasionally decreases in intensity, the colloidal gold reaction also tends to manifest improvement, and sometimes becomes practically negative. Often it is changed from a typical parietic to an atypical syphilitic-zone curve. The Wassermann test of the spinal fluid shows little change until many months have elapsed.

The spirochetes found in the central nervous system of human subjects are heat resistant and chemo-resistant organisms. The diseases which these organisms cause are eminently chronic. Therefore a program of treatment for any of these diseases to be effective must be drawn up with due consid-

eration of the chronicity of the disease and the increased resistance of the treponemas. Fever therapy should be followed by courses of tryparsamide combined with bismuth or mercury. This adjunctive treatment should be continued until the spinal fluid becomes and remains negative.

ARTHRITIS

Definite clinical improvement has followed the use of foreign protein therapy in the treatment of arthritis. The fever which invariably accompanies such methods is frequently quite variable in degree as well as in duration. Therefore, in 1931 Markson and Osborne⁸ introduced electropyrexia as a treatment of arthritis with the idea that much better and more lasting effects might be secured, if the fever was produced by a means subject to better control. We had reason to believe that the peripheral circulation might undergo definite and prolonged improvement. The use of the plethysmograph measuring finger volume changes by Johnson, Osborne and Scupham⁹ supported this belief. Such was the rationale for its introduction.

Arthritis is a disease of obscure etiology, and often difficult to classify. As a result, we find many conflicting reports as to the value of fever therapy. We possess no common standard of criteria of improvement, which naturally complicates an evaluation of the therapeutic results.

It is believed that the therapeutic results depend to a large extent on the type of case selected. The hypertrophic, or degenerative type, should be excluded entirely because of the high incidence of associated cardiorenal damage present in these patients. They do not tolerate electropyrexia well and are subject to such accidents as myocardial failure and fibrillation. We select our patients solely from the infectious (atrophic) group, and this younger group of patients withstands fever without serious danger or discomfort.

There seems to have been no uniformity in regard to the degree and duration of the fever induced by various investigators. Our observations indicate that as a rule the fever induced should not be lower than 103.5° F nor higher than 104° F. This generalization, however, does not hold when treating patients whose obvious reactions to such a temperature are poor as evidenced by a decided malaise from treatment to treatment. Hence, experience and clinical judgment are essential to the effective use of fever therapy.

The number of hours the fever was maintained has varied quite markedly. We have maintained temperatures of 103.5° to 104° F for periods of four and of eight hours. Our best results have been secured with the eight hour period. The results secured with the four hour curve have not been as good nor were they maintained as well. Therefore we favor the use of an eight hour period, unless the patient's reactions indicate otherwise.

The treatment should be given once weekly and the number of treat-

ments to be given will vary with the individual. Our observations indicate that never less than eight treatments should be given, and that probably much better results may be obtained when an average of 20 are administered. Some investigators have given as few treatments as an average of three per patient. Hench¹¹ in 1936 summarized all published reports. He found that of a total of 315 patients with chronic atrophic arthritis treated by fever, only 5 per cent became symptom free, 25 per cent were notably relieved, and the remainder received little or no relief. We feel that if 30 per cent of these cases treated so diversely were notably relieved, the therapy is well worth while.

In our experience, the clinical improvement of these patients is not rapid but on the contrary is very gradual from week to week. The most marked improvement is usually evident about three months after a course of treatments. From this time on the improvement is often continued for some considerable time.

Arthritic patients who show evidence of poor vasomotor balance should be subjected to fever therapy with some degree of caution. Such patients are more liable to manifest shock and circulatory failure. The therapy is not contraindicated in these cases, but they should be treated with caution. Moreover, such patients should not be subjected to too rapid a cooling-off process at the termination of the treatment.

No single treatment has ever yielded the therapeutic results to be desired in arthritis, and one cannot expect that fever therapy alone will be sufficient. It would seem worth while to continue the use of other measures along with fever therapy, though such a policy obviously renders the evaluation of fever therapy difficult.

GONORRHEAL ARTHRITIS

Carpenter, Boak, Mucci and Warren¹² found the thermal death time of 130 strains of gonococci in vitro to vary from 106° to 107° F, the duration of the heat applied varying from six to 27 hours. A patient may be infected with more than one strain, but the patient and his consort will generally have the same strain. Strains showing a marked difference of thermal death time generally indicate a new infection superimposed on an old one. Articular strains are somewhat less resistant to heat than urethral strains. Therefore gonorrheal arthritis may subside before an associated urethritis. The ideal procedure in these cases, therefore, would be to ascertain the thermal death time of the organisms and to produce a corresponding degree of fever. Fever at 106° to 107° F for five to 17 hours has been advocated by Warren, Carpenter and Boak¹³. They also claim that good results were obtained when a fever of three-fourths to one-half the thermal death time was given. Of course, the routine estimation of thermal death time is not always practical. A fever of 106.7° for five hours is frequently used and repeated if found necessary. Usually two to six treat-

ments are required and are given at from three to five day intervals. Hench¹¹ has published the following statistics on 182 cases reported in the literature. One hundred and twenty-eight cases or 70 per cent were more or less promptly "cured," becoming symptom free. About 15 per cent more were markedly improved and about 10 per cent received little or no benefit. Desjardins, Stuhler and Popp¹⁴ state that it is more difficult to obtain cures in female than in male patients.

Bierman and Horowitz¹⁵ have combined fever therapy with additional pelvic heating. They produced a fever of from 105° F to 106° F, and then by means of a vaginal electrode secured a localized temperature of 111° F, which was maintained for three hours. They claim a cure for 19 of 23 patients treated in this manner.

Acute gonorrhea has been frequently treated with fever, but we believe that in the acute stage such a procedure is not indicated. Any form of therapy for gonorrhea which offers the slightest danger to life, is believed to be unwarranted.

MULTIPLE SCLEROSIS

The most extensive observations on the treatment of multiple sclerosis with electropyrexia were carried out by Neymann and Osborne,¹⁶ who reported their results on 25 patients. They classified their patients as mild, advanced, and far advanced. Forty-four per cent of the patients treated showed marked improvement, while an additional 40 per cent were improved to a lesser degree. They held out but slight hope of improvement in the far advanced types, the treatment of such patients entails a risk that one is hardly justified in taking.

The temperature in multiple sclerosis should under no circumstances be permitted to exceed 105° F, due to the danger of upsetting the heat regulatory mechanism and thus inducing heat stroke. A satisfactory fever for these patients is 103.5° F for a period of from six to eight hours. The treatment should be terminated immediately, regardless of the duration of treatment, when the pulse exceeds 160 per minute, when the respiration is very rapid and shallow, or when marked cyanosis is present. With multiple sclerosis these danger signs demand prompt consideration and action on the part of the physician. Treatment is given once a week and the number of treatments required will vary, but will probably average between 20 and 30.

ASTHMA

Hyperpyrexia will not cure asthma, but it does have a very definite place in the treatment of asthma. Several reports have appeared since Feinberg, Osborne, and Afremow initiated the use of this procedure in 1931. Feinberg et al¹⁷ have summarized their results on 42 patients. They selected cases that had failed to respond to the usual methods of treatment and had been under their care for from a few months to several years. These severe

chronic and intractable asthmatics had one or more complicating pulmonary conditions such as emphysema, marked bronchitis or bronchiectasis. Fifty-one per cent of these patients manifested complete remission lasting from several days to 10 months, 29 per cent were improved without manifesting remission. These observers pointed out that remissions may be delayed for two or three weeks after treatment, and expressed the opinion that their results would probably have been more favorable if less severe cases had been selected.

Phillips¹⁸ has recently made a study of 250 patients during an observation period of from six months to three years, but does not state his results.

These two groups of investigators used different techniques. Feinberg et al. used a fever of 104° F, lasting for eight hours and given at a four-day interval, two treatments constituting a course. When the patient's condition did not permit such a fever, then a temperature of 103.5° was maintained for six hours. Improvement was observed even when only the lower fevers were employed.

The temperature should not exceed 105° F. The treatment should be given with the patient sitting in bed, reclining on a back rest, however, those who are able to be fully recumbent without discomfort are treated in that position. It is good practice to have a hypodermic syringe containing adrenalin immediately available so that it can be given without delay in case an attack is precipitated. Ice water or even very cold water should not be given because it may induce an attack.

Phillips¹⁸ advocates the use of lower temperatures, from 101° to 102° F, given biweekly or weekly, the course amounting to at least 10 treatments. He maintains the temperature for from four to five hours.

CHOREA MINOR

The treatment for Sydenham's chorea has always been symptomatic. The disease has been recognized as being self-limited and as disappearing in from two to six months. Sutton and Dodge¹⁹ have used typhoid vaccine for the purpose of producing therapeutic fever in patients with chorea, and reported excellent results. These workers have since used physical measures in preference to the foreign protein method. Following their work Neymann, Blatt and Osborne,²⁰ using electropyrexia, have reported on the treatment of Sydenham's chorea. Of the 25 patients in their series, the disease was very severe in 9, moderately severe in 6, and comparatively mild in 10. The average period of hospitalization was less than 16 days, and the average number of treatments was less than four. The shortest period of hospitalization was five days with two treatments. These children were observed from five to 20 months after discharge from the hospital. Only three recurrences were observed.

Patients with acute carditis as a complication must be treated very cautiously. In such patients the first treatment should be of shorter dura-

tion and the temperature peak lower than in cases of uncomplicated chorea. The temperature in these cases should be maintained at 104° F for eight hours. Temperatures of 105° F or above should not be used because of the danger of convulsive seizures. The treatments can be given twice weekly.

The justification for subjecting patients having a disease with a tendency to cardiac involvement, to fever therapy is that if the recurrence of chorea can be prevented by this method of therapy, a crippling carditis may be prevented, since it is not only the first attack but also the subsequent attacks that affect the heart. In the second place it is desirable to shorten the number of hospital days or the period of confinement in the home, and the records of other investigators²² in this field seem to demonstrate that these aims are accomplished.

The following table gives a summary of technic for treatment of the various diseases discussed.

TABLE II
Summary of Technic

Disease	Fever Curve		Approximate Number of Treatments	Frequency of Treatments	Selection of Cases
	Degrees F	Duration in hours			
Arthritis	104 104	8 5	8-20	Weekly	Infectious (rheumatoid, proliferative)
Complication of gonorrhea	106.7	5	1-3	Weekly	G. C. arthritis, chronic urethritis, prostatitis, etc.
Asthma	104	6-8	2	2nd treatment 3 days later	Intractable Asthma
Multiple sclerosis	104	6-8	20	Weekly	Not too far advanced
General paresis	104 for 6 then increase 106 for 2		20	2 Weekly	Early paretic and not too badly demented patients
Sydenham's chorea	104	6-8	2-10	2 Weekly	Avoid cardiac complications unless well compensated

BIBLIOGRAPHY

1. MEHRTE'S, H. G., and POUPOURIT, P. S. Hyperpyrexia produced by baths, *Neurol and Psychiat*, 1929, **xvii**, 700.
2. MERRIMAN, J. R., and OSBORNE, S. L. Methods of producing hyperpyrexia by various physical agents, *Ill Med Jr*, 1933, **lxiv**, 237-241.
3. NEWMAN, C. A., and OSBORNE, S. L. Artificial fever produced by high frequency currents, *Ill Med Jr*, 1929, **lvi**, 199.
4. NEWMAN, C. A., and OSBORNE, S. L. The physiology of hyperpyrexia, *Am Jr Syph and Neurol*, 1934, **xviii**, 18.

- 5 GIBSON, J, KOPP, I, and EVANS, W A Paper read before First International Fever Conference, New York, 1937
- 6 SCHMIDT, M, HOLMQUEST, H J, and MARSHALL, J G Fever therapy A simplified technic for inducing fever by electromagnetic induction, *Physiotherapy Rev*, 1936, xvi, 97
- 7 BESSEMANS, A, and THIRY, U Nouveaux essais d'application de la thermotherapie locale au traitement de la syphilis primaire et secondaire chez l'homme, *Bruxelles med*, 1933, xiii, 299
- 8 MARKSON, D E, and OSBORNE, S L The treatment of arthritis by sustained fever therapy, *Ill Med Jr*, 1931, lx, 397-403
- 9 JOHNSON, C A, OSBORNE, S, and SCUPHAM, G Studies of peripheral vascular phenomena The effect of artificial fever on the pulse volume changes of the fingers, *Am Jr Med Sci*, 1935, clxxx, 485
- 10 NICHOLS, E H, and RICHARDSON, F L Arthritis deformans, *Jr Med Res*, 1909, xxi, 149-221
- 11 HENCH, P S, BAUER, W, FLETCHER, A A, GHRIST, D, HALL, F, and WHITE, T P The problems of rheumatism and arthritis Review of American and English literature for 1935 Third rheumatism review, *ANN INT MED*, 1936, x, 754-909
- 12 CARPENTER, C M, BOAK, R A, MUCCI, L A, and WARREN, S L The studies on physiologic effects of fever temperatures, thermal death time of *Neisseria gonorrhoea* in vitro with special reference to fever temperatures, *Jr Lab and Clin Med*, 1933, xviii, 981-990
- 13 WARREN, S L, CARPENTER, C M, and BOAK, R A The thermal death time of 130 strains of *Neisseria gonorrhoea* Report of 5th Ann Fever Conference, May, 1935
- 14 DESJARDINS, A W, STUHLER, L G, and POPP, W C Fever therapy for gonococcic infections, *Jr Am Med Assoc*, 1935, civ, 873
- 15 BIERMAN, W, and HOROWITZ, E A General hyperthermia with heat localization by radiotherapy in the treatment of pelvic inflammatory disease, *New York State Med Jr*, 1933, xxxiii, 218
- 16 NEYMANN, C A, and OSBORNE, S L The treatment of some multiple sclerosis by electropyræxia, *Jr Nerv and Ment Dis*, 1934, cxlix, 423-433
- 17 FEINBERG, S M, OSBORNE, S L, and STEINBERG, M J Sustained artificial fever in the treatment of intractable asthma, *Jr Am Med Assoc*, 1932, lxxviii, 801-806
- 18 PHILLIPS, K M Hyperpyrexia in bronchial asthma, *Arch Phys Ther, X-Ray and Rad*, 1936, xvii, 282-288
- 19 SUTTON, L P The treatment of chorea by the induction of fever, *Jr Am Med Assoc*, 1931, lxxvii, 299-301
SUTTON, L P, and DODGE, K The treatment of chorea by induced fever, *Jr Pediat*, 1933, iii, 813-876
- 20 NEYMANN, C A, BLATT, M L, and OSBORNE, S L The treatment of chorea minor by means of electropyræxia, *Jr Am Med Assoc*, 1936, cvii, 938-942
- 21 KRUSEN, F H The present status of fever therapy produced by physical means, *Jr Am Med Assoc*, 1936, cvii, 1215-1221
- 22 Transactions of International Fever Conference, New York, 1937

THE PATHOLOGY AND MECHANISM OF ANAPHYLAXIS *

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A SURVEY of recorded studies on anaphylaxis and on shock reveals the remarkable fact that neither of these conditions has been investigated by the methods of pathology. Probably this was because this type of circulatory phenomenon was interpreted as a functional disturbance having no morphologic basis. The belief that postmortem examinations in such conditions reveal no significant changes, apparently had not been questioned.

It has become apparent recently that a combination of the methods of pathology with those of physiology may produce pertinent evidence. It has been shown^{17 a, b, 18} that shock, occurring clinically or produced experimentally in various ways, is associated with characteristic tissue changes which are etiologically related to the mechanism of its development. A similar study of anaphylaxis has revealed significant facts which give a broader comprehension of the mechanism of that phenomenon. In it, as in other conditions of disease, correct interpretations find corroboration in the accompanying morphologic changes. The discussions here will be limited to the mechanism of anaphylaxis, its morphologic features and its relationship to shock otherwise produced.

It is assumed that the reader is conversant with the various phases of anaphylactic phenomena, their conditions of occurrence, and related matters. Details of these will be found in reviews by Wells, Karsner, Zinsser, Topley and Wilson, and Seegal.

FUNCTIONAL DISTURBANCES

The signs of anaphylaxis in dogs are pruritus, increased respiratory rate, dyspnea, rapidly falling blood pressure, salivation, vomiting, diarrhea and urination. The vomitus is frothy and mixed with bile. In severe cases these discharges contain blood. The heart beats rapidly, even violently. There are ataxia, marked weakness, and sometimes convulsions. The pupils dilate and the eyes become dull. Death appears imminent but it seldom occurs within two or three hours and often is delayed 24 hours or longer. It has been found that immediate death may be produced in dogs by proper adjustment of the dosage.

The symptoms of human anaphylaxis or allergy are similar to those of dogs. In mild cases there are itching, restlessness, and the development of a skin rash or wheals. In severe cases there are generalized urticaria, erythema, dyspnea, cyanosis, edema of the face, tongue and throat, cough and

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expectoration of frothy sputum Vomiting and defecation may occur The blood pressure falls and the pulse becomes rapid and weak Recovery or collapse and death may follow In some cases asthmatic features are prominent There is obvious similarity between these manifestations of anaphylaxis in dogs and man and those of shock produced by other means in these same species

The bio-chemical and hematologic features which accompany anaphylaxis are essentially identical with those of traumatic or experimental shock Seegal's review of this subject records the following changes in the chemistry of the blood of animals in anaphylaxis The lactic acid and the sugar content are increased, likewise the urea, creatinine and non-protein nitrogen The alkali reserve is decreased, the ptyease ferment is increased and its antiferment decreased (Jobling) Karsner's review states that the viscosity of the whole blood is increased and the sedimentation speed of the corpuscles decreased Dean and Webb found a rise in the hemoglobin and red cell count following shock doses of horse serum into sensitive animals The hemoconcentration was proportional to the severity of the symptoms In severe reactions the blood chlorides are decreased (Major, Friedmann and Frankel) The recorded observations on the blood sugar content in anaphylactic shock agree that it is increased This applies to peptone poisoning as well

The temperature first rises, then falls rapidly (Richet) But in prolonged, sublethal or chronic anaphylaxis the temperature increased in varying degrees In serum sickness, in extensive necrosis or abscess following Arthus phenomenon, and in allergic reactions—"hay fever" for example—the temperature rises

Dean and Webb found moderate leukopenia as represented by a reduction of the leukocytes to 25 per cent of the normal number The maximum reduction was reached in about half an hour, and was followed by a marked leukocytosis Richet found an intense leukocytosis ranging from 30,000 to 90,000 in 'chronic anaphylaxis,' i.e. those experiments in which death was delayed 10 to 48 hours It is significant to note in this connection that Dale et al. found a marked leukopenia in fatal histamine shock while, in our own observations,^{17 (3)} smaller injections of histamine were followed by leukocytosis in cats, monkeys and man MacKenzie and Hanger's review on serum sickness records a moderate leukocytosis in that condition

There is evidence of variations in coagulability similar to those reported in leukocytic counts Seegal's summary shows that the coagulation of the blood is delayed in guinea pigs, dogs and rabbits Shattuck recorded a similar finding in human cases of serum sickness and of chronic urticaria He cited similar observations by Biedl and Krause and by Pepper and Krumbhaar His observations indicated that this resulted from retarded prothrombin activity Weil found that blood from dogs in anaphylactic shock would remain unclotted for many hours or even days On the other hand, Witzinger and many others have shown that the *first injection* of

horse serum in man is followed by a marked *acceleration* in the speed of coagulation. This reaction finds a common clinical application in such injections for the control of persistent bleeding. Witzinger noted also that reinjection of horse serum after a delay of several days was followed by *retarded* coagulation time.

Each of the physiologic disturbances listed above occurs similarly in poisoning with peptone, in traumatic shock, and in anaphylaxis. Also in each of these, there are features which vary with the acuteness or stage of the condition. The coagulability of blood is high in early stages but decreases later, there is leukopenia in the severe early acute reactions followed by leukocytosis in later stages, an increase in temperature accompanies subacute reactions, but a fall in temperature occurs in severe or fatal cases. The similarity of these variations in traumatic shock, in poisoning with peptone and in anaphylaxis indicate a fundamental similarity in those conditions. There is lack of evidence concerning the mechanism which produces the variations.

ASSOCIATED PATHOLOGIC CHANGES

I have made several detailed reports^{17 (1, 2)} on the visceral changes found in shock. These were drawn from examinations of human cases following death from surgical or traumatic shock, burns, abdominal emergencies such as obstructions, perforations and acute pancreatitis, severe intoxications and other clinical conditions which led to circulatory collapse. Similar conditions were reproduced experimentally in dogs and identical circulatory changes were found post mortem in their viscera. These will be stated briefly for purposes of comparison with the visceral appearances found after death from anaphylaxis.

The respiratory and gastrointestinal mucosae are purplish-red, edematous and contain hemorrhagic flecks. The lungs are deeply congested, frequently they are edematous and contain ecchymoses. The pleurae, pericardium, peritoneum and meninges are congested, often they contain petechiae, and serous effusions are common. The liver and kidneys show diffuse congestion and acute parenchymatous degeneration. Capillary hemorrhages are seen in the brain and in other tissues. Characteristically the spleen is contracted and relatively bloodless.

The changes described result from atony and dilatation of the capillaries and venules which become relaxed, dilated and engorged with blood. This dilatation increases greatly the volume-capacity of the vascular system. The permeability of the endothelium becomes abnormally increased resulting in edema of tissues and in serous effusions. The leakage of plasma into the tissues increases the concentration and decreases the total volume of the blood. The combined effects of these processes produce a disparity between the blood volume and the volume-capacity of the circulatory system. This results in a progressive circulatory deficiency manifested in the syndrome of shock.

The earliest observations on anaphylaxis in animals record the same type of congestive, edematous and hemorrhagic changes in the viscera which we have found regularly in clinical and experimental traumatic shock. Portier and Richet (1902) noted in dogs "There is intense congestion with interstitial hemorrhages in the whole gastrointestinal tract. The lungs are congested and sometimes also the endocardium and pleura." Gay and Southard (1908) found hemorrhages in one or more organs in 34 out of 41 guinea pigs following fatal anaphylaxis. These were most numerous in the gastrointestinal tract and the lungs, and were found occasionally in the adrenals, kidneys, pericardium and brain. They noted a similarity to the endotheliolysis produced by snake venoms. The authors regarded these findings as highly significant but did not advance any hypothesis concerning the origin of them. However, they emphasized that an acceptable explanation for anaphylaxis must also explain the congestive and hemorrhagic features observed. Coca (1909) noted congestion and many small hemorrhages in the lungs, and many dilated capillaries and venules were seen microscopically. Pearce and Eisenbrey (1910) described marked congestion of the viscera, numerous petechiae in serous surfaces and large ecchymoses in the gall-bladder and in the gastrointestinal mucosae following anaphylaxis in dogs. Weil confirmed the previous observations on visceral congestion and hemorrhages both in peptone poisoning and in anaphylactic shock in dogs. He noted parenchymatous degeneration, and in one instance marked necrosis, of hepatic cells. The livers in each instance were intensely congested, swollen and cyanotic.

Karsner (1912) studied the gross and microscopic changes in the lungs of guinea pigs following anaphylaxis. His observations were made on 52 animals sensitized to blood serum from various species. The gross and microscopic findings were of the same character in each group. Regularly the lungs were congested and contained hemorrhages. Microscopically they showed engorged capillaries, hemorrhages, and many of them were edematous. Conglutination thrombi such as usually accompany stasis were seen frequently in the minute vessels. These observations were made long before the significance of such changes accompanying shock was recognized. He drew no conclusions concerning the mechanism and significance of these circulatory changes.

Manwaring and his associates found pronounced splanchnic engorgement and cyanosis with hemorrhagic lesions in the intestinal mucosa both following peptone poisoning and following anaphylaxis in dogs. There were characteristic hemorrhagic lesions in the intestinal mucosae with edema of the intestinal villi followed by desquamation and superficial necrosis in the later stages. There was free blood in the lumina of the bowels. There was marked congestion but little hemorrhage after mild anaphylaxis. They believed that these effects were due to the action of a poison, formed in the liver, which had a histamine-like effect on the extrahepatic vascular structures. This effect accounted for the low blood pressure which

was regularly present. Similar circulatory changes were noted by Petersen and his associates, by Gurewitsch and by others.

We produced acute anaphylaxis in rabbits, guinea pigs and dogs in order to make observations on visible changes in the viscera. These confirmed the findings previously recorded. Visceral congestion, petechial hemorrhages and ecchymoses were present regularly when death occurred promptly, and the same features plus tissue edema when death was delayed. The following is a representative example.

A dog, weighing 8.4 kg, was sensitized by 50 cc of horse serum injected subcutaneously and three days later by 50 cc given intravenously. Fifteen days later 200 cc of horse serum were slowly injected intravenously. This produced immediate distress and severe illness. There were convulsions, the respirations became rapid and shallow and the pulse rapid and weak. The dog passed large quantities of liquid feces and of urine. There was a free flow of saliva. A period of apathy and collapse preceded death which occurred within 15 minutes after the injection.

Postmortem findings. The pleura and pericardium were moderately congested and the peritoneum extensively congested. No excess of fluid and no hemorrhages were present in the serous cavities. There were hemorrhages beneath the peritoneum about the ileo-cecal region. The minute vessels along the mesenteric attachment were engorged and unusually prominent.

The heart appeared normal except that its chambers contained almost no blood. The lungs were moderately congested as were also the mucosae of the trachea, bronchi and gall-bladder.

The liver was extremely congested. Blood dripped freely from the cut surfaces. The substance of the kidneys was similarly congested.

The mucosa of the stomach was moderately, and that of the duodenum was extremely congested. It had the appearance of purple velvet. The lumen of the small bowel contained blood tinged fluid. The lining of the large bowel and of the bladder were moderately congested. The spleen was dry, firm and bloodless. The pancreas and adrenals appeared normal.

On histologic examination the liver cells showed marked parenchymatous degeneration, some of them were necrotic, and the vessels were markedly engorged. There were extreme congestion and minute extravasations in the gastrointestinal mucosae. Moderate parenchymatous degeneration and congestion were seen in the renal cortex. The splenic pulp was relatively anemic.

Exactly similar changes were found in other dogs following anaphylaxis. It was noted that when death occurred within a few minutes no edema was seen, whereas after delayed death edema was regularly present in the lungs, respiratory mucosae and in the gastrointestinal lining. Frequently there were petechial hemorrhages in the mucous and serous surfaces and occasionally there was fluid in serous cavities. These observations were made in rabbits, guinea pigs and dogs. The same changes resulted from injections of peptone, extracts of various normal tissues and from histamine. At this point it should be emphasized that the changes described are characteristic of shock produced experimentally by various means.

Similar evidences of circulatory disturbance are recorded following death from serum injections in man. In the case reported by Boughton, death resulted in 45 minutes after the injection of one minim of horse

serum into a hypersensitive person. The necropsy examination revealed intense injection of the minute vessels throughout the abdominal viscera, especially in the stomach, small bowel, mesentery, gall-bladder and appendix. The parietal peritoneum was markedly congested. Both lungs were emphysematous and contained areas of hemorrhage. There were petechiae in the pericardial surfaces and the kidneys were markedly hyperemic. The microscopic examination showed pulmonary hyperemia and hemorrhages, hyperemia, hemorrhages and edema of the kidneys, small hemorrhages in the myocardium and adrenals, and edema of the hepatic cells.

Lamson's review of cases of sudden death following injection of foreign proteins contains only a few details of postmortem examinations. Congestion of the brain, meninges, liver, kidneys, gastrointestinal mucosae, general stasis, emphysema and congestion of the lungs were the changes noted. Bullowa and Jacoby reported the necropsy findings in a child after an injection of anti-diphtheritic serum. The blood in the great vessels was unclotted and was small in amount. There was marked congestion of the cerebral surfaces, the meninges, lungs, liver, adrenals, kidneys and spleen. Parenchymatous degeneration of hepatic cells was noted.

I have had opportunity to make postmortem observations in only one case of this kind. A negro youth 18 years of age developed meningitis of the epidemic type and was given antimeningococcic serum intravenously. He promptly developed respiratory distress, and circulatory failure was followed by death in a few minutes. There was no history obtainable regarding any previous injection of horse serum. The necropsy was made by Dr. D. R. Morgan who kindly allowed me to examine the organs. There were intense congestion, edema and hemorrhages in the lungs, respiratory mucosae and lining of the gastrointestinal tract, also intense congestion of the liver and kidneys. The spleen was small, flabby and relatively bloodless.

From the available evidence it appears that the indications of circulatory disturbance seen in the tissues after death from anaphylactic shock are of the same character and distribution as those after experimental or clinical traumatic shock. One is led to believe that the mechanism of circulatory disturbance and death in these conditions is similar.

THE MECHANISM OF ANAPHYLAXIS

Two interpretations have been considered as explanations for the phenomena associated with anaphylaxis. The earlier interpretation was that the reaction between antigen and antibody occurs in the circulating blood and/or in the tissue fluids, and gives rise to a toxic substance—'anaphylatoxin'—whose effects on various cells of the body produce the characteristic syndrome. Several serious objections have rendered this theory untenable. The incubation of antibody with antigen *in vitro* does not produce a potent injurious product. The precipitate resulting from such a combination is

relatively innocuous. The simultaneous injection of antibody and antigen does not produce shock in nonsensitized animals. In passive sensitization an interval of several hours must elapse before the injection of the antigen will produce characteristic symptoms. Evidently such results are not explainable as taking place in the blood itself.

Other evidence incompatible with the anaphylatoxic theory was supplied by Gay and Southard (1908). They showed that if all the blood from a sensitized animal is replaced by blood from normal animals of the same species, the animal still remained sensitive. The injection of antigen into such an animal produced characteristic anaphylactic reactions. This observation was confirmed by others. Schultz showed that organs whose vessels had been washed clean of blood by perfusion with salt solution, still responded characteristically to the introduction of the antigen. A bit of excised uterine musculature from an animal sensitized to horse serum will contract vigorously when a minute amount of horse serum is added to the fluid in which the strip of muscle is suspended. Muscle from a non-sensitized animal gives no such response when similarly treated. This reaction, confirmed by Dale, Weil and others, has become a standard method for determining sensitivity.

These facts together with others led to the interpretation that the reactions which produce the manifestations of anaphylaxis take place, not within the body fluids but within the tissue cells. That the reactions are not due to any toxicity of the antigen-antibody combination itself, or of its derivatives, but to disturbances within tissue cells arising from the combination of antigen and antibody within or upon them.

Cells are irritated when antigen and antibody meet within them. The resulting disturbances of function vary with the physiology of the cells within which they meet. Smooth muscle cells contract, as shown in the classic test for sensitivity in which guinea pig uterine muscle is used. Mucous cells discharge their secretion, as shown when antigen is applied to the membranes of a sensitized animal. The gastrointestinal mucosae discharge mucus and fluid more freely, as shown in the diarrhea which often accompanies anaphylaxis. Glands secrete more actively, as indicated by the excessive salivation which accompanies anaphylaxis in dogs. Petersen and his associates believed that the active mobilization of enzymes, which is associated with anaphylaxis, originates from the stimulated or injured cells such as endothelium, liver, pancreas and others. Capillaries lose their tonus and the endothelium becomes more permeable when subjected to anaphylactic irritation. This was shown by perfusion experiments (Manwaring) and by the development of tissue edema both in systemic and in local anaphylaxis. Opie interpreted the extensive edema which develops in anaphylaxis as due to the meeting of antigen and antibody within the endothelial cells. The resulting injury caused increased permeability of the capillary walls.

Severe anaphylactic irritation to the cells results in parenchymatous

changes as shown in the myocardium, liver and kidneys by histologic examination. When the irritation is more severe, necrosis results and the Arthus phenomenon is produced. An inflammatory reaction, noted by many and studied particularly by Opie, results when antibody meets its antigen in the tissues.

The systemic disturbances are manifestations of the sum total of the cellular effects. These vary in different species and seem to depend upon the type of cells most affected in a particular species. In guinea pigs the chief manifestation results from broncho-spasm, in rabbits vasculo-spasm, and so on. But in *each species* there is evidence also of *endothelial injury*. Seegal's review of the subject led her to conclude that most of the symptoms of anaphylactic shock in the various animals, are referable to one or the other of two causes: *contraction of smooth muscle* and *increased capillary permeability*.

Petersen and his associates noted an increased flow of lymph when dogs sensitized to egg albumin received that substance by injection. This lymph was rich in fibrin, globulin and albumin which indicated that it resulted from leakage through capillary walls. No increased flow of lymph followed the injection of egg albumin into non-sensitized dogs. They interpreted this as definite evidence of endothelial injury which took place immediately following the injection, and as evidence that the endothelium is the point of attack of the injuring agent in anaphylaxis. If recovery took place the endothelium became less susceptible to subsequent injections and a refractory state resulted. They concluded that shock of the endothelium is a primary factor in producing the symptoms of acute anaphylaxis.

Manwaring and his associates stressed the importance of the liver as the seat of anaphylactic injury in dogs, but their final interpretation was stated as follows: "We believe that the increased capillary permeability thus demonstrated will ultimately be shown to be the dominant physiologic change in protein sensitization, to which all other anaphylactic reactions are secondary."

Lewis emphasized capillary permeability as the major factor in anaphylaxis and attributed it to the release of H-substance by tissue cells injured by the combination of antigen-antibody. It is questionable whether this explanation applies to all instances in which urticaria develops. Without questioning the validity of his conclusions concerning the 'triple response' following mechanical and other forms of injury to tissue cells, I propose an alternate explanation for the urticaria of protein sensitivity. Lewis explains it as resulting from the injurious effects of the antigen upon the sensitized *tissue* cells which, in response to that injury, release H-substance thereby producing the triple response. The alternate explanation is that *not only* the *tissue* cells but also the *capillary endothelial* cells are sensitized and consequently are directly injured by contact with the antigen. These two concepts are presented visually in the accompanying diagram.

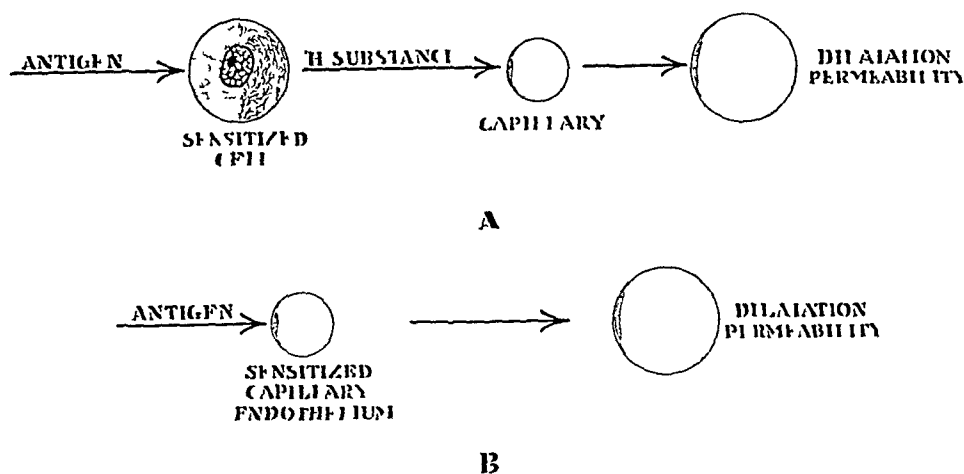


FIG 1

(A) Illustrates the mechanism proposed by Lewis. Antigen acting on *sensitized cells* causes the release of H-substance which causes adjacent capillaries to dilate and to become permeable.

(B) Illustrates the direct effect of antigen upon *sensitized capillary endothelium* with the same result.

If the mechanism were indirect, as believed by Lewis, anaphylaxis should be gradual in onset. Horse serum injected intravenously does not come in contact with tissue cells immediately. Normal capillary endothelium is relatively impervious to serum, and most of it remains for a relatively long time in the blood. Field and Drinker were able to detect traces of horse serum in the lymph of dogs, only after an interval of one or two hours following its intravenous injection. The full effect of an injection of horse serum into a sensitized animal would not be felt until the serum had slowly penetrated the capillary membranes and had entered the tissue cells.

The explosive promptness of anaphylaxis in a highly sensitized animal suggests a *direct*, rather than indirect, mechanism. I have seen death occur within 10 minutes following the intravenous injection of horse serum into sensitized dogs. Lamson's review of anaphylactic deaths in man showed that in 40 such cases, death occurred within an hour in 33, within 15 minutes in 28 and within 5 minutes in many cases. Wells cited a case in which a man, who previously had received injections of tetanus antitoxin, was transfused from a donor who that very morning had received an injection of anti-toxic serum. Death occurred within a few seconds. Such reactions are too prompt to be explained satisfactorily by the indirect mechanism proposed by Lewis. The view that such results are from the *direct* effect of antigen upon *sensitized endothelium* is in perfect consonance with the accepted interpretation that the tissue cells constitute the seat of the anaphylactic reaction. The view merely *includes endothelial cells* among the tissue cells affected.

WHEELS, INFLAMMATION AND SHOCK

It is pertinent at this point to emphasize an essential physiologic relationship between wheal formation (the 'triple response' of Lewis), inflammation and shock. I have been unable to find a single exception to the following generalization: *Those agents which when applied to the skin evoke an urticarial reaction, will likewise evoke acute inflammation when applied to normal tissues. The same agents will produce typically the syndrome of shock if their effects are exerted systemically.* For examples, mechanical trauma to the skin is followed by wheal formation (Lewis), if more extensive it is followed by inflammation, severe extensive mechanical trauma results in shock. Histamine produces a wheal when a minute amount is applied in the skin, and produces acute inflammation when introduced into living tissues, when a sufficient quantity is injected intravenously, shock is the result. Heat suitably applied to the skin produces the 'triple response,' and is followed by inflammation, an extensive superficial burn will cause shock. A minute amount of antigen produces a wheal in the skin of a sensitized subject and will produce local inflammation (Arthus' phenomenon) of the tissues under suitable conditions, the injection of a sufficient amount of protein into a subject sensitized to it, will produce shock. The same observations apply to a wide variety of agents including chemical poisons such as HgCl_2 , arsenicals et al., sepsine, emetine, peptone and extracts of tissue, bile and cholic salts, the poisons of actinia and other marine animals, bee-sting poison, snake venoms, diphtheria toxin and other bacterial products.

The essential factor in the reaction to all such agents is injury to capillary endothelium produced either directly or, as postulated by Lewis, indirectly through the agency of a substance released by the tissue cells in response to the injury. Wheal formation results from the local effects of vascular dilatation and permeability. These are the circulatory changes of acute inflammation. The leukocytic phenomena of inflammation are produced by substances liberated by injured cells.^{17 (3)} When similar dilatation and permeability of capillaries and venules are produced in extensive visceral areas, they result in a circulatory deficiency which manifests itself in the syndrome of shock.

SUMMARY

The physiologic disturbances accompanying anaphylaxis are of the same character as those of poisoning with peptone, and those of traumatic shock. The gross and microscopic visceral changes are of the same character after death from each of these conditions. These observations indicate that the underlying mechanisms are related.

The anaphylactic reaction is cellular rather than humoral in location. The meeting of antibody and antigen within the cells irritates or injures them and causes increased functional activity if the injury is mild. If

severe it results in an inflammatory reaction not different from that which follows other injuries

There is evidence that the capillary endothelium is a chief point of injury in anaphylaxis. The capillaries respond to this, as to other injuries, by loss of tonus and increased permeability. Anaphylactic shock probably results from the direct effect of the antigen upon the sensitized endothelial cells, rather than indirectly by injury to tissue cells which by liberating H-substance cause capillary dilatation.

The development of skin wheals, tissue inflammation and systemic circulatory failure in anaphylaxis, is significantly similar to wheals, inflammation and shock following trauma and other injuries to living tissues. The fundamental capillary reactions in these respective phenomena are identical.

BIBLIOGRAPHY

- 1 BOUGHTON, T H Anaphylactic death in asthmatics, *Jr Am Med Assoc*, 1919, **lxviii**, 1912
- 2 BULLOWA, J G M, and JACOBI, M Fatal human anaphylactic shock, report of case with autopsy, observations and review of literature, *Arch Int Med*, 1930, **xlvi**, 306-315
- 3 COCA, A F Die Ursache des plotzlichen Todes bei intravenoser Injektionen artfremder Blutkorper, *Virchow's Arch*, 1909, **cxcvi**, 92
- 4 DALE, H H The anaphylactic reaction of plain muscle in the guinea pig, *Jr Pharm and Exper Therap*, 1912, **iv**, 167
- 5 DEAN, H R, and WEBB, R A Blood changes in anaphylactic shock in dog, *Jr Path and Bacteriol*, 1924, **xxvii**, 65-79
- 6 FIELD, M W, and DRINKER, C K Permeability of capillaries of dog to protein, *Am Jr Physiol*, 1931, **xcvii**, 40-51
- 7 FRIEDMANN, U, and FRANKEL, E Ueber Veränderungen der Wasser- und Kochsalz ausscheidung während der Serumkrankheit, *Verhandl d deutsch Gesellsch f inn Med*, 1921, **xxxi**, 400
- 8 GAY, F P, and SOUTHARD, E E Further studies in anaphylaxis, *Jr Med Res*, 1907, **xvi**, 143, 1908, **xix**, 17
- 9 GUREWITSCH, N A Über den reflektorischen und den toxischen Gefassshock, *Arch f clin Chir*, 1931, **clvi**, 401-411
- 10 JOBLING, J W, PETERSEN, W F, and EGGSTEIN, A A The mechanism of anaphylactic shock, *Jr Exper Med*, 1915, **xxii**, 401
- 11 KARSNER, H T The lungs of the guinea pig in anaphylaxis produced by toxic sera, *Immunitatsforsch u exper Therap*, 1912, **xiv**, 81 *Bacteriology and immunology*, 1928, chapter **lxviii**, Jordan and Falk, University of Chicago Press
- 12 LAMSON, R W Sudden death associated with injection of foreign substances, *Jr Am Med Assoc*, 1924, **xcii**, 1091-1098
- 13 LEWIS, T Blood vessels of the human skin and their responses, 1927, Shaw and Sons, London
- 14 MACKENZIE, G M, and HANGER, F M Serum disease and serum accidents, *Jr Am Med Assoc*, 1930, **xciv**, 260
- 15 MAJOR, R H Studies of blood chemistry in allergy, *Bull Johns Hopkins Hosp*, 1923, **xxiv**, 104-108
- 16 MANNWING, W H, CHILCOTE, R C, and HOSEPIAN, V M Capillary permeability in anaphylaxis, *Jr Am Med Assoc*, 1923, **lxv**, 303-309
- 17 MOON, V H (1) The shock syndrome in medicine and surgery (2) Shock, a definition and differentiation (3) Mechanism of acute inflammation, *ANN INT MED*, 1935, **viii**, 1633 *Arch Path*, 1936, **xxii**, 325, *ibid*, 1935, **xx**, 561

- 18 MOON, V H, and KENNEDY, P J Pathology of shock, Arch Path, 1932, xiv, 360-371
- 19 OPIE, E L Desensitization to local action of antigen (Arthus phenomenon), 1924, ix, 247-268 Inflammation and immunity Jr Immunol, 1929, xvii, 329-342
- 20 PEARCE, R M, and EISENBREY, A B Anaphylactic shock in the dog, Jr Infect Dis, 1910, vii, 565
- 21 PETERSEN, W F, JAFFE, R H, LEVINSON, S A, and HUGHES, T P Endothelial permeability, endothelium in canine anaphylactic shock, Jr Immunol, 1923, viii, 323-349 Jr Biol Chem, 1925, lxi, 179
- 22 PORTIER, P, and RICHEL, C De l'action anaphylactique de certains venins, Compt rend Soc d biol, 1902, liv, 170
- 23 RICHEL, C Anaphylaxis, 1913, Liverpool University Press
- 24 SCHULTZ, W H Physiologic studies in anaphylaxis, Jr Pharm and Exper Therap, 1912, iii, 299
- 25 SEEGAL, B C Agents of disease and host resistance, by Gay, F P et al, 1935, Thomas, Baltimore, chapter vi
- 26 SHATTUCK, H F Protein intoxication, Arch Int Med, 1917, xx, 167
- 27 TOPLEY, W W C, and WILSON, G S Principles of bacteriology and immunology, 1936, Wm Wood and Co, Baltimore
- 28 WEIL, R (1) The nature of anaphylaxis and the relations between anaphylaxis and immunity (2) Studies in anaphylaxis, Jr Med Res, 1912, xlvii, 497, 1914, xxx, 87, 299 Anaphylaxis of dog, Jr Immunol, 1917, ii, 399, 525
- 29 WELLS, H G Present status of problems of anaphylaxis, Physiol Rev, 1921, i, 44 Chemical pathology, 1925, W B Saunders, Philadelphia, p 220-235
- 30 WITZINGER, O Zur anaphylaktischen Analyse der Serumkrankheit, Ztschr f Kinderheilk, 1911, iii, 211
- 31 ZINSSER, H Resistance to infectious diseases, 1931, 4th ed, Macmillan, New York

EXPERIENCES IN TREATING TOXIC GOITER IN A LARGE PUBLIC HOSPITAL *

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THE treatment of disease in a large public hospital presents unique problems. The Cook County Hospital, in which this study was made, has 3200 beds and its patients represent, for the most part, the poorest element in the city of Chicago. The conditions in the hospital with regard to the staff, interns, nurses, diet and crowding are about the same as in most similar institutions. Disease is seen more in its advanced than in its early stages, and in the case of toxic goiter, a large number of severe cases of long standing are observed in markedly undernourished individuals. It is of interest to observe whether these factors preclude the establishment of a low operative mortality rate in this disease.

The mortality from operations for goiter in this hospital has been summarized in a previous communication to this College.¹ For the years 1931, 1932 and part of 1933 it was 13.1 per cent for exophthalmic goiter, 9.8 per cent for toxic adenoma, 4.1 per cent for non-toxic adenoma and 2.6 per cent for simple goiter. Among factors responsible for these high mortality rates may be mentioned (1) inadequate preoperative and postoperative care, with lack of good judgment in selecting the time of operation, and (2) too frequent relegation of operative procedures to surgeons who lacked the special training requisite for thyroid surgery. It was common practice for patients to be operated on from seven to ten days after starting iodine, regardless of other considerations. Patients were placed on the usual ward diet which was, for them, very inadequate in calories, and they often lost weight on it. The time of operation was often decided, not by the attending man, but by the senior intern. The infrequency of checking the condition of the patient with metabolism tests may be gauged from the fact that there was one unsatisfactory basal metabolism machine for the whole hospital of 3200 beds, and that only a few tests were done each day by a technician who also had the responsibility of the electrocardiographic laboratory. The fluid used for parenteral administration, because of its method of preparation, usually produced severe reactions, almost uniformly causing chills, fever, and redness and swelling of the part into which it was injected. In some instances records indicate that reactions from fluid may have contributed to the death of the patient, particularly when given intravenously.

* Read before the Twenty-Second Annual Session of the American College of Physicians, New York, April 8, 1938.

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We began our work in the latter part of 1932. It was neither possible nor desirable that we should have control of all the patients with goiter in the hospital. From 1933 on we observed nearly half of them. The remainder served as a control for a few years, and later on in modified degree, after the ideas developed exerted some influence throughout the whole hospital. We are very grateful to the various members of the staff who co-operated with us to make this study possible. The hospital has made an important contribution by permitting us, with few exceptions, to keep patients in the institution as long as seemed desirable to prepare them for operation.

We began by treating each patient as an individual problem. Perhaps the most important principle adopted was the withholding of surgery until the condition of the patient justified operation, regardless of how long this took. It is our contention that the battle is commonly won or lost before any operative procedures are carried out and that in most instances a crisis in the postoperative period means inadequate preoperative preparation. We have not been greatly concerned with the length of time that iodine was administered before operation, often extending it to many weeks in spite of an increase in basal metabolism. In general, the other factors concerned offset this risk. Until the fluid for parenteral use was improved, we prohibited its administration unless specially prepared fluid was obtained outside the hospital.* A special high caloric diet for patients with toxic goiter was developed and operation was rarely resorted to unless the patients gained weight. Another important consideration was that we gradually gained more control over the selection of surgeons.

RESULTS

It will be necessary to group toxic adenoma and exophthalmic goiter together under the general heading "toxic goiter." In our own series a distinction was made between the two diseases, but in the case of other observers, the diagnosis of toxic adenoma was made too frequently, usually by the intern. We have gone through all the hospital records for the years 1931-33 and tried to establish the true proportion of toxic adenoma to exophthalmic goiter for these years. So far as we could tell, it was about 1 case of toxic adenoma to 3 of exophthalmic goiter (1 to 3½ in our own series), and this ratio probably holds throughout succeeding years.

We have summarized the mortality rates in patients who were under our care and those who were not, in tables 1 and 2 and in figure 1. In 1931, just before our work began, there were 16 deaths following 159 thyroidectomies for toxic goiter—a mortality of 10.1 per cent. During the period

* Some time after the work was started we began distilling small amounts of water for the preparation of fluid for parenteral use in our own laboratory, and for many months this was the only source in the hospital of water suitable for such purposes. This function was later taken over by Dr. Fantus. Making good fluid available to all the patients in the hospital has, in our opinion, been one of the major therapeutic improvements of the last few years.

TABLE I
Mortality from Thyroidectomy, Cook County Hospital—Our Series

Year	TOXIC GOITER (ALL CASES)					EXOPTHALMIC GOITER				TOXIC ADENOMA			NON TOXIC GOITER			ALL TYPES		
	Num ber of Pa tients	Num ber of Opera tions	Num ber of Deaths	Opera tive Mor tality Per cent	Num ber of Opera tions	Num ber of Deaths	Opera tive Mor tality Per cent	Num ber of Opera tions	Num ber of Deaths	Mor tality Per cent	Num ber of Opera tions	Num ber of Deaths	Mor tality Per cent	Num ber of Opera tions	Num ber of Deaths	Mor tality Per cent	Num ber of Deaths	Mor tality Per cent
1932	8	8	0	0 0	6	0	0 0	2	0	0 0	1	0	0 0	9	0	0 0	0	0 0
1933	64	69	2	2 9	60	2	3 3	9	0	0 0	12	0	0 0	81	2	2 5	2	2 5
1934	47	52	4	7 7	45	4	8 9	7	0	0 0	6	0	0 0	58	4	6 9	4	6 9
1935	62	65	0	0 0	42	0	0 0	20	0	0 0	28	0	0 0	93	0	0 0	0	0 0
1936	68	71	3	4 2	46	2	4 1	22	1	4 5	22	0	0 0	93	3	3 2	3	3 2
1937	51	52	0	0 0	39	0	0 0	12	0	0 0	19	1	5 3	71	1	1 4	1	1 4
1932-37	300	317	9	2 8	228	8	3 3	72	1	1 4	88	1	1 1	405	10	2 5	10	2 5
1932-34	119	129	6	4 7	101	6	5 4	18	0	0 0	19	0	0 0	148	6	4 1	6	4 1
1935-37	181	188	3	1 6	127	2	1 5	54	1	1 9	69	1	1 4	257	4	1 6	4	1 6

1932-37 there were 54 deaths following 572 thyroidectomies for toxic goiter in patients whom we did not have charge of—a mortality of 9.4 per cent. During the same period there were 9 such deaths following 317 thyroidecto-

TABLE II
Mortality from Thyroidectomy, Cook County Hospital—Series of Other Observers

Year	TOXIC GOITER			NON-TOXIC GOITER			ALL TYPES		
	Number of Operations	Number of Deaths	Mortality Per cent	Number of Operations	Number of Deaths	Mortality Per cent	Number of Operations	Number of Deaths	Mortality Per cent
1931	159	16	10.1	36	2	5.6	195	18	9.2
1932	149	19	12.8	48	1	2.1	197	20	10.2
1933	85	12	14.1	47	2	4.3	132	14	10.6
1934	89	4	4.5	69	4	5.8	158	8	5.1
1935	102	8	7.8	56	0	0.0	158	8	5.1
1936	72	5	6.9	45	1	2.2	117	6	5.1
1937	75	6	8.0	25	0	0.0	100	6	6.0
1931-37	731	70	9.6	326	10	3.1	1057	80	7.6
1932-37	572	54	9.4	290	8	2.8	862	62	7.2
1932-34	323	35	10.8	164	7	4.3	487	42	8.6
1935-37	249	19	7.6	126	1	0.8	375	20	5.3

mies for toxic goiter in patients whom we did have charge of—a mortality of 2.8 per cent. The number of cases is not large enough for the mortality rates to be significant on a yearly basis, but they naturally divide themselves into two groups (a) those up to the end of 1934, and (b) those in the period 1935-37. In February 1935 a new ward was opened in the hospital in which about 10 beds were allotted to us for the study of patients with goiter. Since that time we have had better control over the preoperative and postoperative care of our patients and have been able for the most part to restrict operations to a few men with a special interest and training in thyroid surgery. In the earlier period, 1932-34, there were 35 deaths following 323 thyroidectomies for toxic goiter in patients who were not under our care—a mortality of 10.8 per cent, and during the same period there were 6 deaths following 129 such operations in patients who were under our care—a mortality of 4.7 per cent. In the later period, 1935-37, there were 19 deaths following 249 thyroidectomies for toxic goiter in patients not under our care—a mortality of 7.6 per cent, whereas following 188 such thyroidectomies in patients under our care, there were 3 deaths—a mortality of 1.6 per cent. In other words, our mortality has been less than one-fourth as great as in the rest of the hospital during the later period, and less than one-third as great during the whole period 1932-37.

During the first period when the mortality rate for all our cases of toxic goiter was 4.7 per cent as compared with 10.8 per cent for other observers, we were able to control the preoperative and postoperative care to a considerable extent, but had very little choice of surgeons. During the

second period, when our mortality rate was 1.6 per cent compared with 7.6 per cent among other cases, we were able to control the preoperative and postoperative care still better, had developed more conservatism about the time of operation, and were able to restrict the operations to a smaller number of more experienced surgeons. Thus, our mortality of 1.6 per cent in the second period of the study may be compared with the mortality of 10.8

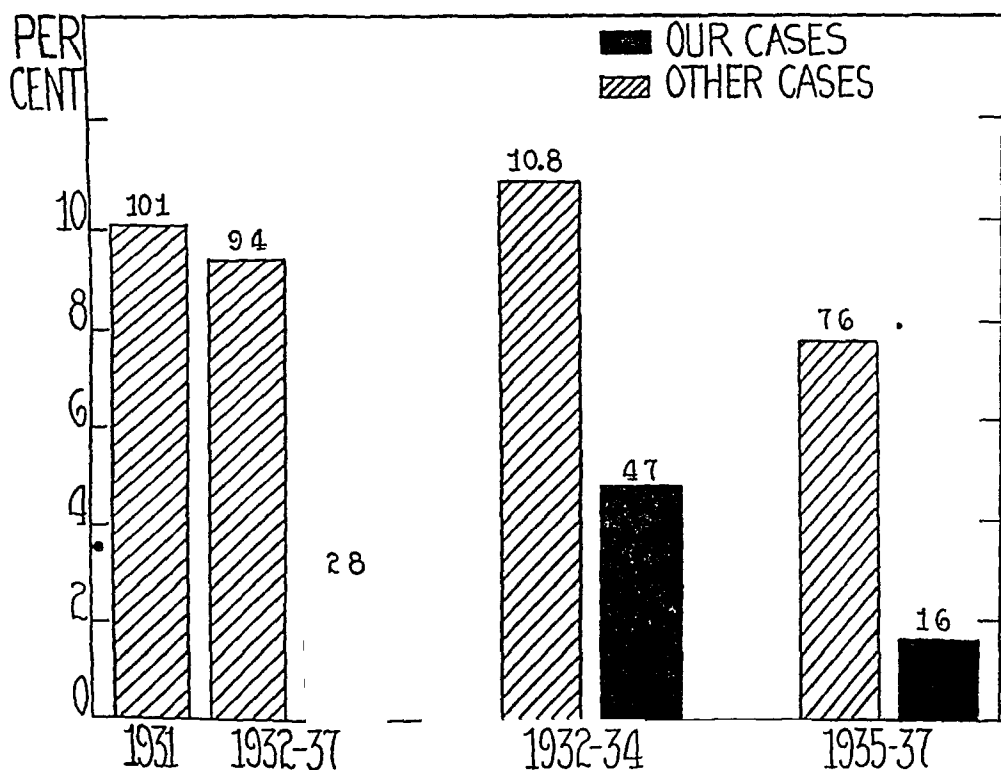


FIG 1 Comparison of surgical mortality rates in patients with toxic goiter under our care, and those not under our care

per cent for the rest of the hospital at the beginning of the study in order to give a better idea of the reduction that it has been possible to bring about. It is to be noted that in the last three years there has been some reduction in mortality among the patients we have not had charge of. This may be attributed in some degree to a change of attitude in the hospital as a whole toward the management of goiter, and to elimination of the severe reactions from fluid used parenterally. There is no doubt in our minds that the mortality for the hospital as a whole can be reduced to less than 2 per cent with careful supervision. In order to bring this about, however, the management of all patients with goiter should be turned over to a small group of individuals who are specially qualified to carry this out. The policy of letting many surgeons get a very limited experience in operating on patients with toxic goiter, together with the policy of keeping hospital beds free for use by quick turn-over of these patients on the medical wards, will inevitably maintain a high mortality rate.

It is also of interest to consider the mortality following operations for non-toxic goiter, which was largely of the adenomatous type. During the period 1932-37 there were 8 deaths in 290 patients not under our care—a mortality of 2.8 per cent—whereas during the period 1932-37 there was 1 death in 88 patients under our care—a mortality of 1.1 per cent. We do not have a sufficiently large number of cases to divide into two periods. During the period 1932-34 there were 7 deaths in 164 patients of other observers (4.3 per cent) whereas during 1935-37 there was 1 death in 126 patients (0.8 per cent). An important factor in the high rate during the first period was 4 deaths among their 69 patients in 1934 (5.8 per cent), a fact which is probably a coincidence, because during the same year they had their lowest mortality rate for toxic goiter.

CAUSES OF DEATH

It is instructive to review the causes of death in our patients with toxic goiter. A brief analysis of them is given in table 3. Eight of the nine patients who died had exophthalmic goiter and one, toxic adenoma. Only two of the nine patients died of a crisis. In one (Mr F. D.), death occurred seven hours after an unusually long operation involving much trauma. We did not consider the patient to be in very good condition for surgery at the time (1934) and at present would not permit operative procedures in a similar case. The other postoperative crisis developed in a thin, apathetic man (Mr S. L.) in whom exophthalmic goiter was complicated by diabetes mellitus. He appeared, however, to be doing fairly well three to four days after operation, only to become worse in association with the development of pneumonia, from which he died five days after operation.

Three patients died from pneumonia. One (Mr J. K.), had a chill at midnight and a temperature of 100.2° F. at 5 a. m. the morning of operation. These signs were unfortunately not detected by the intern and the patient had been in good condition when we saw him the night before. Another man (Mr C. P.) had had an upper respiratory infection which had supposedly cleared up by the time of operation, but after a careful review of his case, it is questionable whether he was completely well. In the third patient (Mrs F. B.) there appeared to be no doubt that a fulminating bronchopneumonia was caused by unauthorized intratracheal anesthesia, which a resident in the nose and throat department was trying out, for removal of a substernal toxic adenoma. The tube was left in several hours after the operation and the patient died about 25 hours afterward.

One man 60 years old (Mr A. N.) who suffered from arteriosclerotic heart disease and had previously been in the hospital with cardiac decompensation, was convalescing satisfactorily until he suddenly became unconscious 10 days after operation and died three hours later, probably from either a cerebral or coronary accident.

It is noteworthy that three patients died from sudden respiratory difficulty within 30 hours of operation. In two (Mr C. F. and Mrs M. C.),

TABLE III
Analysis of Deaths Following Thyroidectomy for Toxic Goiter, in Our Series

Patient	Age Yrs	Diagnosis	BASAL METABOLIC RATE Per cent normal				Thyroidectomy	Length of Time Death Occurred After Operation	CAUSE OF DEATH
			On Admis- sion	Level During Rest	During Adminis- tration of Iodine				
					Lowest Level	Level Before Operation			
Mr C P	53	Exophthalmic goiter Arteriosclerosis	+57	+54	+26	+33	Subtotal 11/10/33	2½ days	Bronchopneumonia (Upper respiratory infection apparently not entirely cleared up at time of operation)
Mr S L	52	Exophthalmic goiter	+49	+51	+27	+30	Subtotal 12/15/33	5 days	Thyroid crisis and pneumonia
Mr A N	60	Diabetes mellitus Exophthalmic goiter Arteriosclerosis	+37	+20	+ 1	+21	Subtotal 3/ 5/34	10 days	Cerebral or coronary accident (Sud- denly became unconscious and died 3 hours later)
Mr F D	40	Chron. myocarditis Emphysema Exophthalmic goiter	+60	+38	+40	+55	Left hemi- thyroidectomy 3/13/34	7 hours	Thyroid crisis
Mrs L T	31	Exophthalmic goiter	+54	+41	—	—	Subtotal 3/17/34	13 hours	Pressure of hematoma on collapsible trachea
Mr C F	41	Exophthalmic goiter	+39	+46	+32	+32	Subtotal 11/10/34	4½ hours	Sudden respiratory difficulty Probably bilateral cord paralysis
Mrs M C	47	Exophthalmic goiter	+65	+42	+14	+14	Subtotal 3/23/36	24 hours	Sudden respiratory difficulty from bila- teral cord paralysis produced at opera- tion
Mrs F B	51	Toxic adenoma (sub- sternal)	+25		+20	+20	Subtotal 5/ 2/36	25 hours	Bronchopneumonia (Unauthorized in- tratracheal anesthesia)
Mr J K	56	Exophthalmic goiter Cirrhosis of liver	+36	+18	— 1	— 1	Subtotal 8/20/26	4 days	Bronchopneumonia (Temperature 100 2° F at 5 a m morning of operation)

this was apparently associated with bilateral paralysis of the vocal cords, and in one (Mrs L T) was apparently caused by pressure from a hematoma on a collapsible trachea

In retrospect, it would appear that the deaths in eight of these nine patients might have been prevented. The development of pneumonia in two patients might have been avoided by more careful search for an upper respiratory infection before operation, and in the third patient, we think would not have occurred if intratracheal anesthesia had not been used. The rather sudden death in the 60 year old man, ten days after operation, can scarcely be attributed to the operation itself, and probably would have occurred without it. The two crises might have been avoided by withholding surgery until the patients were in still better condition for operation. The three deaths from sudden respiratory difficulty were the result of purely surgical complications and could have been prevented by having adequate facilities for immediate passage of a life-saving tube, followed by tracheotomy. It is desirable that every patient have a special nurse for 48 hours following a thyroidectomy, so that emergencies may be detected as soon as they arise.

The single death among our patients with non-toxic goiter occurred in a woman of 37 with a large substernal goiter. A pack was not inserted as ordered by the surgeon and she developed a large hematoma in which an infection developed, leading to cellulitis of the neck, mediastinitis, bronchopneumonia, gangrene of the lung and finally death 23 days after operation. This again was a purely surgical complication.

We think it is significant that since 1934 not a single patient with toxic goiter of whom we have had charge has died of a postoperative crisis. This would appear to be largely the result of the great care used in preparing these patients for operation.

FACTORS INFLUENCING OPERATIVE MORTALITY

Operative mortality is determined by (a) the condition of the patient, and (b) the skill of the surgeon.

GENERAL PREOPERATIVE MANAGEMENT

In previous communications we have discussed in some detail the various factors concerned in getting the patient into the best possible condition for operation^{1, 2, 3}. These may be summarized as follows:

- 1 *The Administration of Iodine* Within very wide limits the size of the dose and the form in which it is administered are not important^{2, 4}. No longer do we necessarily follow the old dictum of carrying out operation from 10 to 14 days after starting iodine. All other factors known to be important in determining the outcome must be taken into consideration.

- 2 *Rest* It is very important that this be properly regulated. In order to preserve muscle tone and prevent patients from becoming bedridden, rest

must not be complete except in the presence of cardiac decompensation or a thyroid crisis, and then only until the emergency has passed

3 *A Diet Sufficiently High in Calories to Produce a Gain in Weight*
For most patients this means the administration of 4000 to 5000 calories a day. The regular high caloric diets of most hospitals are not adequate

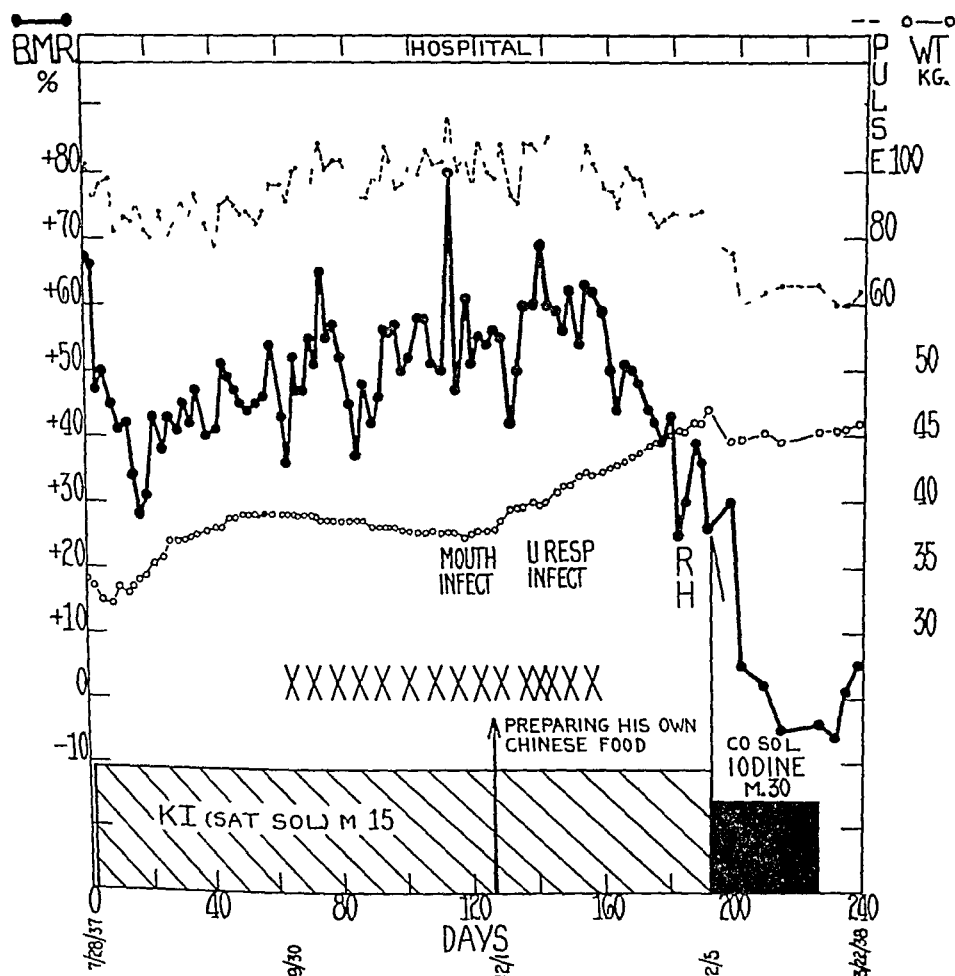


FIG 2 Management of severe exophthalmic goiter in a very emaciated Chinaman (H B T Ht 161 cm Age 40 yrs). Although there was at first a marked initial reduction in basal metabolism during the administration of iodine, he weighed only 34 kg. Note effect of catering to his dietary habits, and of using roentgen-ray therapy (X). Throughout the whole period preceding final gain in weight he was too weak to stand operative procedures. At time of operation (right hemithyroidectomy) he was in good condition and had only a moderate postoperative reaction.

for this purpose because they contain only about 3200 calories. It is usually unwise to operate unless weight is gained. Sometimes attention to details of dietary habits may be a life-saving measure. This is illustrated by a Chinaman (figure 2) who spoke English poorly and disliked our food. He weighed only 71 pounds and it was impossible to produce a sufficient increase in his weight until we let him get his own supply of rice and cook it to his taste in our laboratory.

4 *Roentgen-Ray Treatment in Patients with High Metabolic Rates, Refractory to Iodine*

5 *The Administration of Digitals in Cardiac Decompensation*

Favorable signs in predicting the outcome of operation are (1) Gain in weight, (2) Reduction in emotional instability and increase in muscle strength, (3) Reduction in basal metabolism during the administration of iodine, (4) Absence of upper respiratory infections, and (5) Absence of cardiac decompensation. With a well marked gain in weight there occurs a reduction in emotional instability and an increase in muscle strength, whether the basal metabolism drops or not.

It is usually safe to perform a thyroidectomy when

- 1 The basal metabolism has dropped to plus 40 per cent or lower during the administration of iodine and the patient has gained 10 pounds or more in weight

- 2 Emotional instability and muscle weakness are slight or when both have decreased markedly in association with a gain in weight of 10 pounds or more, even though the basal metabolism has dropped very little

- 3 Cardiac decompensation, present on admission to the hospital, has completely disappeared, provided other factors are favorable. When edema is present on admission, loss of weight as a result of its disappearance must be taken into consideration in gauging the real change in the patient's weight

It is ideal when, at the same time, the basal metabolism drops to within nearly normal limits, the weight increases and emotional instability and muscle weakness decrease markedly. However, such an ideal combination of favorable signs is encountered in only a small percentage of the patients.

In our experience it is usually unwise to operate when

- 1 The patient fails to gain or is losing weight

- 2 Emotional instability and muscle weakness are marked⁵

- 3 The basal metabolism is plus 60 per cent or higher, in spite of the administration of iodine

- 4 The disease is increasing rapidly in severity⁶

- 5 Less than two weeks has elapsed after an upper respiratory infection has cleared up

- 6 Cardiac decompensation is present

A thyroidectomy is never an emergency procedure and when done as such often results in the death of the patient. The single most important principle is never to carry out surgical procedures until the condition of the patient has improved sufficiently to warrant them. The death of a patient is almost never caused by taking an adequate length of time for preoperative preparation. An example of the length of time occasionally necessary to prepare patients is illustrated in figure 2.

MANAGEMENT OF PATIENTS REFRACTORY TO TREATMENT

While we have developed certain general rules to aid us in deciding when a patient will or will not withstand surgical procedures, the decision in an individual case is not always easy. In an attempt to cover all possible contingencies we prefer to err on the side of conservatism. We can always delay an operation, but once a crisis has set in usually nothing will stop it. A certain proportion of patients are very difficult to prepare for operation for one reason or another, the failure commonly being associated with little or no reduction or even with a rise in metabolism during the administration of iodine. Sometimes in spite of a reduction in metabolism, patients fail to gain weight and continue to have marked muscle weakness and emotional instability. It is necessary to devise some method of preparing these poor risk patients for surgery. We have used roentgen-ray treatment, giving commonly one treatment at weekly intervals for a total of about twelve treatments. Because of some increase in the severity of the disease following each treatment, it is unwise to give them at shorter intervals. An example of what may be accomplished by roentgen-ray therapy is illustrated in figure 3.

By paying great attention to preoperative preparation, multiple stage operations can usually be avoided. However, whenever there is any doubt about how extensive surgical procedures the patient will tolerate, it is wise to do the operation in at least two stages. In rare instances we have resorted to ligations to test the ability of the patient to withstand surgery, although we doubt whether they have any other value.

IMPORTANT POINTS IN THE IMMEDIATE PREOPERATIVE PREPARATION OF THE PATIENT

In addition to the more prolonged period of preparation for operation, it is important in the period immediately preceding operation.

- 1 To make a careful search for an upper respiratory infection or a sudden increase in the severity of the disease just before the patient goes to the operating room
- 2 To administer a carbohydrate meal from six to eight hours before operation. This helps to prevent acidosis in the postoperative period and is more important than in persons with normal basal metabolism, because of the speed with which patients with toxic goiter burn food
- 3 To administer the regular dose of iodine with this meal
- 4 To institute, at least 24 hours before the scheduled time of operation, some program suitable for the control of emergencies in patients in whom the disease is complicated by diabetes

IMPORTANT POINTS IN THE IMMEDIATE POSTOPERATIVE TREATMENT

In the immediate postoperative period the following points are important

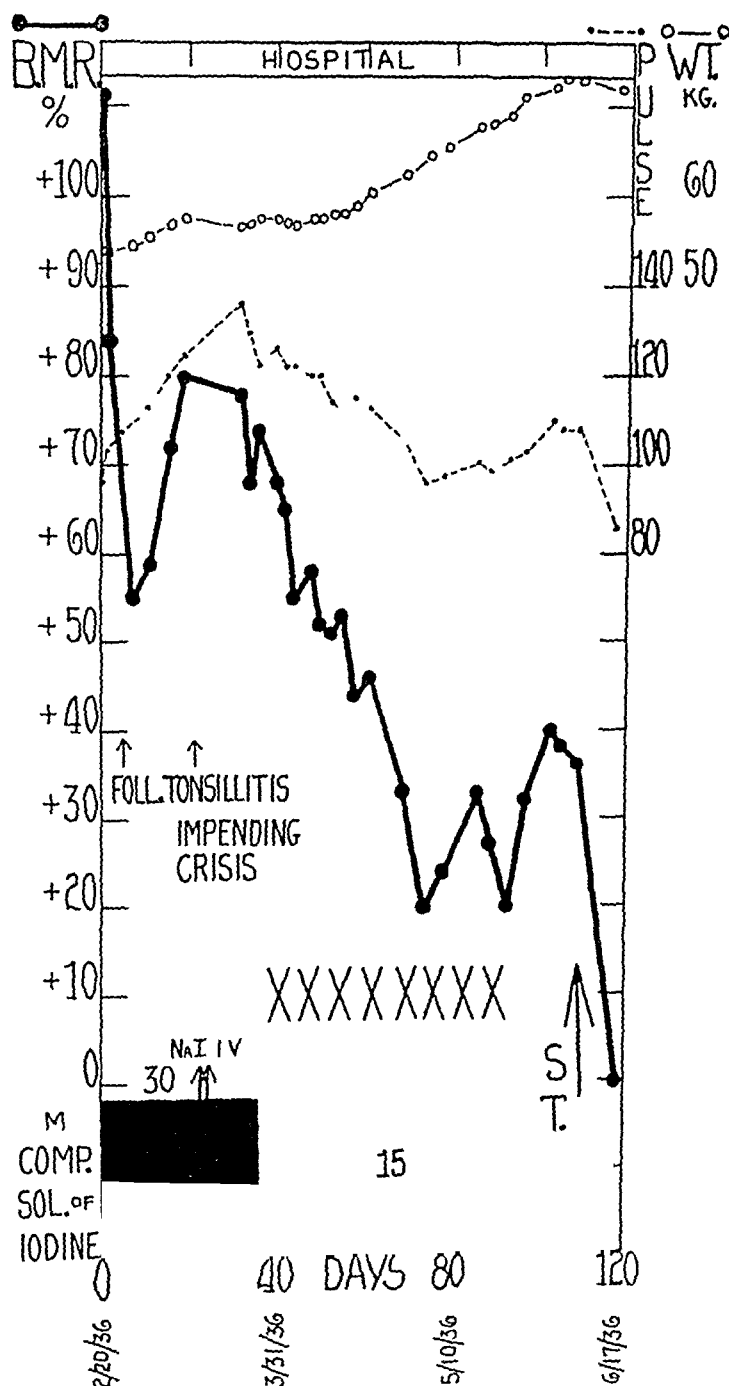


FIG 3 The use of roentgen-ray treatment (X) in preparing a patient with severe, exophthalmic goiter for operation (R R Ht 160 cm Age 30 yrs) Note rapidity of rise in basal metabolism after initial reduction, in association with onset of an upper respiratory infection Great severity of disease, in spite of iodine, precluded operation After marked improvement with roentgen-ray therapy, subtotal thyroidectomy was performed with uneventful convalescence

1 Careful observation of the wound for the early detection of excessive bleeding

2 Careful observation of the patient to detect respiratory difficulty as soon as it arises, either from laryngeal or tracheal obstruction. Usually a paralysis of one vocal cord does not produce serious respiratory difficulty, but in its presence an emergency must be considered to exist until proved otherwise

3 The services of a specially trained nurse for the first 48 hours, to report trouble as soon as it arises

4 Facilities on the ward or in the patient's room for emergency passage of a life-saving tube and performance of a tracheotomy

5 Intravenous administration of a suitable combination of salt and dextrose for prolonged or excessive vomiting, a thyroid crisis or circulatory collapse. When a thyroid crisis is present the continuous intravenous administration of fluid for several days may be a life-saving measure, circulatory collapse sometimes setting in shortly after it is stopped. If patients are properly prepared, most of them do not require the administration of fluid postoperatively by the parenteral route

6 Administration of iodine to control any residual thyrotoxicosis

7 Search for parathyroid tetany on the second to the fourth post-operative day, and its control with suitable measures, if observed

CONDITION OF PATIENT VS SKILL OF SURGEON

The relative importance of the condition of the patient and the skill of the surgeon in the reduction of operative mortality is not easy to determine. As previously pointed out, it was largely by improving preoperative and postoperative management that we were able to reduce the rate from 10.8 per cent to 4.7 per cent. With still further improvement in these two factors and considerable selection of surgeons, we were able to reduce the rate further to 1.6 per cent. During the period 1932-37 three of the best surgeons had 5 deaths in performing 222 thyroidectomies for Thompson and Taylor—a mortality of 2.3 per cent, whereas they had 22 deaths in performing 297 thyroidectomies for other medical men—a mortality of 7.4 per cent. That surgical skill is important is obvious from the records of individual surgeons. Numerous examples of unnecessary complications developing after operation by unskillful men could be cited.

COMMENT

It has been demonstrated that even in a large, crowded, public hospital, where medical care is of the type available on a restricted budget and where the patients are largely from the poorest classes of society and commonly have the disease in its more advanced stages, it is possible to establish a mortality rate from operations for toxic goiter that approaches that obtained

in the best highly specialized thyroid clinics in this country. The medical care, although necessarily not of the quality most desirable, can, if constantly watched, be adequate in all essential elements, and the undernourishment so often noted in the patients can be overcome by special attention to their diet.

If hospitals wish to keep their mortality rates from thyroid surgery at the lowest possible figure, they must be willing to relegate the management of the patients to a group of internists and surgeons who are specially qualified in this field. What has been done in thyroid disease can be done in many other fields, notably that of gall bladder surgery. In all conditions involving surgical procedures, the outcome is determined by the preoperative condition and postoperative care of the patient, and the skill of the surgeon. These factors are not peculiar to thyroid surgery.

SUMMARY

In a large public hospital it has been possible to reduce the mortality rate from operation for all cases of toxic goiter from 10.8 per cent to 1.6 per cent, and for exophthalmic goiter from 13.1 per cent to 1.5 per cent, by paying great attention to the preoperative and postoperative care of the patient and by restricting surgery for the most part to specially qualified men.

The most important factors in causing this reduction appear to have been care in improving the preoperative condition of the patient and postponement of operative procedures until it appeared highly probable that the patient could stand them.

A thyroidectomy is never an emergency procedure and when done as such commonly results in the death of the patient.

A crisis in the postoperative period usually means that the preoperative care has been inadequate.

It is usually unwise to operate when

- 1 The patient fails to gain or is losing weight
- 2 Emotional instability and muscular weakness are marked
- 3 The basal metabolic rate is plus 60 per cent or higher, in spite of iodine
- 4 The disease is increasing rapidly in severity
- 5 Less than two weeks has elapsed after the disappearance of an upper respiratory infection
- 6 Cardiac decompensation is present

Roentgen-ray therapy is sometimes of value in preparing for operation patients who are refractory to other methods of treatment.

In retrospect, it seems probable that nearly all of the deaths in our series might have been prevented. Of nine patients with toxic goiter who died, in only two was the death the result of crisis, and in them the preoperative

condition was poor. In three it was caused by sudden respiratory difficulty, representing a purely surgical complication. In three by pneumonia. And one old man with heart disease died rather suddenly ten days after operation. Deaths from sudden respiratory difficulty can almost always be prevented by having adequate facilities available for immediate relief of the obstruction. The presence of upper respiratory infections must be watched for with the greatest care before operation, because they are an important cause of postoperative pneumonia.

If hospitals wish to keep their mortality rates at the lowest possible level, they must relegate the management of thyroid disease to internists and surgeons who are specially qualified in this field.

BIBLIOGRAPHY

- 1 THOMPSON, W O, TAYLOR, S G III, and MEYER, K A. Factors influencing operative mortality in exophthalmic goiter, *ANN INT MED*, 1934, viii, 350.
- 2 THOMPSON, W O. Factors of importance in the treatment of exophthalmic goiter, *Illinois Med Jr*, 1932, lxi, 520.
- 3 THOMPSON, W O, TAYLOR, S G III, and MEYER, K A. The relation between the pre-operative condition of the patient and operative mortality in exophthalmic goiter, *Illinois Med Jr*, 1935, lxxvii, 53.
- 4 THOMPSON, W O, THOMPSON, P K, and COHEN, A C. The range of effective iodine dosage in exophthalmic goiter. IV. The effect on basal metabolism of the daily administration of about 0.75 mg of iodine, *Arch Int Med*, 1932, xlix, 199.
- 5 MAYO, C H, and PLUMMER, H S. The thyroid gland, 1926, C V Mosby Company, St Louis.
- 6 MALLORY, T B, MEANS, J H, and YOUNG, E L. Exophthalmic goiter and acute rheumatic fever, case no 15472, *New England Jr Med*, 1929, cci, 1056.

TREATMENT OF UNDULANT FEVER, A REPORT OF FIVE CASES TREATED WITH A SPECIFIC POLYVALENT SERUM

By HARRISON F. FLIPPIN, M.D., Philadelphia, Pennsylvania

THE incidence of undulant fever in the United States is steadily on the increase. The United States Public Health Service statistics¹ for 1927 show only 112 cases as compared to 2008 reported in 1935. With this increase in the prevalence of the disease we find numerous reports² dealing with therapy. It is not the purpose of this paper to attempt to evaluate the various forms of treatment but to report five cases of the disease which were effectively treated with a specific polyvalent serum.[†]

The antimelitensis serum used in the treatment of these cases was a sterile polyvalent antiserum of bovine origin with preservative. Two separate groups of cattle were used in the production of the antiserum. One group received, intravenously, ascending doses of heat killed suspensions of *Brucella abortus*. The other group received in the same manner, heat skilled suspensions of *Brucella melitensis*. The cattle received doses of the antigen on three days of each week. The series of injections necessary to produce an agglutinin titer of 1 to 1600 or more against the specific antigen required approximately two months of such treatment. Sera of individual bleedings from each group having sufficient potency, to which 0.35 per cent phenol had been added as a preservative, were pooled and allowed to age. Equal parts of *Brucella abortus* antisera and *Brucella melitensis* antisera were mixed and filtered. The final mixture had an agglutinin titer of 1 to 800 against both *Brucella abortus* and *Brucella melitensis*.

The treatment in these cases varied somewhat at first as to the route of administration and dosage as we were concerned with serum reactions whose severity was then undetermined. We now believe the method of choice is an initial intramuscular injection of 1 c.c. of serum as a test dose followed in 24 hours, if no reaction occurs, by six daily intravenous injections of 50 c.c. of serum. The serum is best given with 100 c.c. of physiological salt solution over a fifteen minute period.

CASE REPORTS

Case 1 G. S., white male, 37 years of age, was admitted May 28, 1935, to Dr. T. Grier Miller's private service, complaining of recurrent attacks of chills, fever and headaches of 13 months' duration. Physical examination was negative, except for a

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From the Hematology Section and the Medical Clinic of the Hospital of the University of Pennsylvania.

† Antimelitensis serum, Sharp and Dohme Lot No. 85872.

palpable spleen There was a moderate leukopenia, negative blood culture, a positive blood agglutination reaction for *Brucella abortus* in a dilution of 1 to 6400, and a

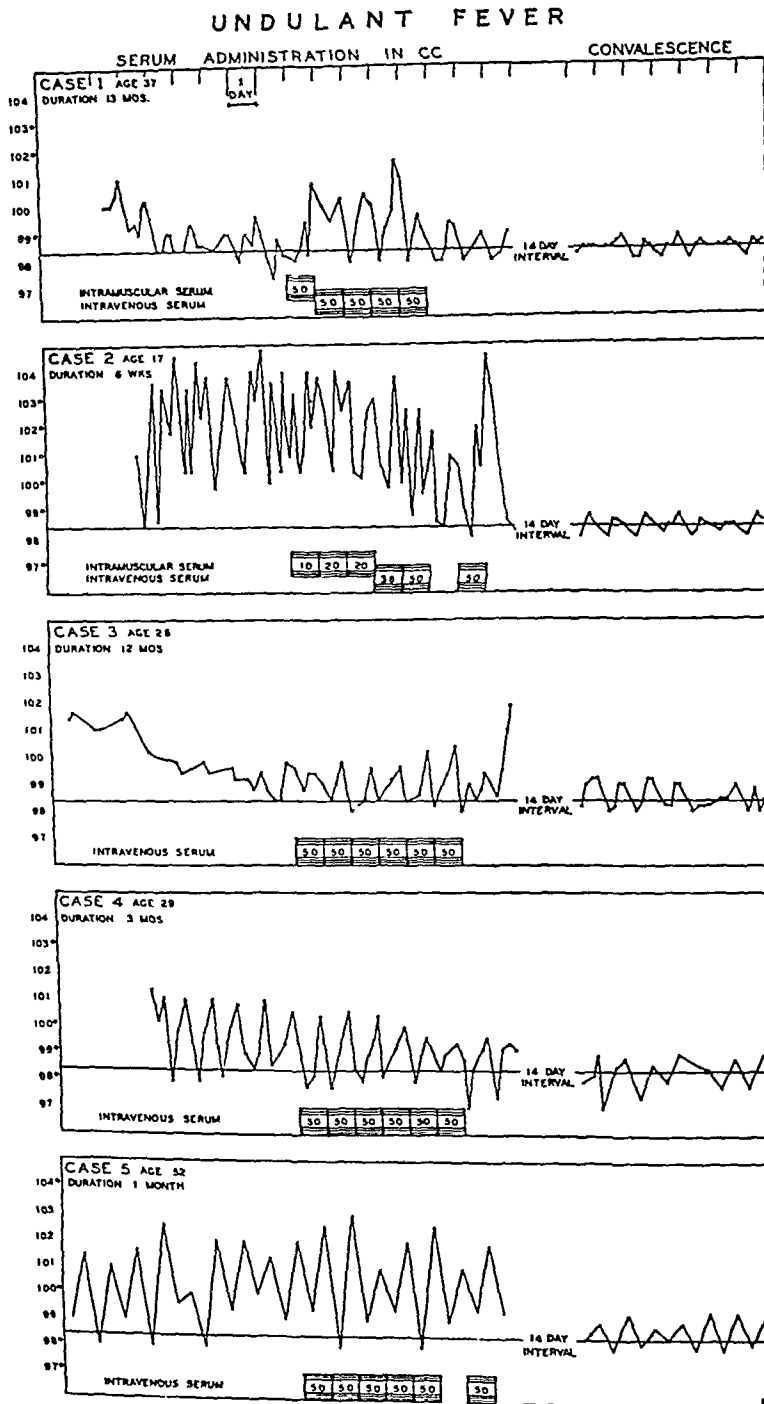


CHART 1 Showing temperature readings and serum administrations

positive skin test for *Brucella abortus* Chart 1 portrays the temperature readings and the time and amounts of serum administered as well as the mode of administration There was a slight elevation of temperature and some itching of the skin fol-

lowing the first 50 c.c. of serum. The patient returned to work two weeks after the completion of this treatment and since then has remained in good health.

Case 2 L. W., white girl, 17 years of age, admitted July 31, 1935 to Dr. T. Grier Miller's private service, with a history of chills, sweats, and fever of four months' duration, during which time there were marked weight loss and weakness. A palpable spleen was the only positive physical finding. There was a moderate secondary anemia, slight leukopenia, negative blood culture, positive blood agglutination reaction for *Brucella abortus* in 1 to 2560 dilution, and a positive skin test for *Brucella abortus*. Temperature readings and serum administration are shown in chart 1. The only evidence of serum sickness was extreme weakness on the fifth day of treatment and for that reason serum was not given for 24 hours. The patient became symptom free within two weeks following the serum and has continued well.

Case 3 M. E., white female, 26 years of age, admitted September 27, 1936 to Dr. Thomas Fitz-Hugh's private service, complaining of weakness, loss of weight, sweats, and fever of 12 months' duration. Physical examination was negative. There was a moderate leukopenia, negative blood culture, positive blood agglutination for *Brucella abortus* in a dilution of 1 to 6400, and a positive skin test for *Brucella abortus*. The temperature readings and serum administration are shown in chart 1. There were no signs or symptoms of serum sickness. The patient became free of symptoms within three weeks after the completion of the serum therapy, and has remained in good health.

Case 4 J. C., white male, 29 years of age, admitted September 24, 1936 to Dr. Alfred Stengel's ward service, suffering with marked weakness, loss of weight, night sweats, chills and fever of three months' duration. Physical examination was negative except for evidence of weight loss and a palpable spleen. There was a moderate secondary anemia, slight leukopenia, negative blood and urine cultures, positive blood agglutination for *Brucella abortus* in a dilution of 1 to 5120, and a positive skin test for *Brucella abortus*. Temperature readings and serum administration are shown in chart 1. There was no evidence of serum sickness. The patient became free of symptoms within two weeks after receiving serum and has remained well.

Case 5 E. F., white male, 52 years of age, admitted November 12, 1936 to Dr. Alfred Stengel's private service, with a history of weight loss, profuse sweats, and fever of one month's duration. Physical examination was essentially negative. There was a moderate leukopenia, negative blood culture, a positive blood agglutination for *Brucella abortus* in 1 to 6400 dilution, and a positive skin test for *Brucella abortus*. Temperature readings and serum administration are shown in chart 1. There was no appreciable serum reaction. Serum was not given on the sixth day due to a misunderstanding. Except for weakness, the patient became essentially free from symptoms within three weeks after serum therapy. Since that time the patient has remained in good health.

DISCUSSION

In this report we have included every case of undulant fever that was treated with serum in this hospital. The duration of illness in these cases was from 1 to 13 months. Aside from the usual routine measures, none of these patients received any other form of therapy than the specific polyvalent serum. The diagnosis was made in all cases by a typical history, a positive skin test, and a positive blood agglutination in high titers for *Brucella abortus*. At this time all five cases are in good health, with apparent cures ranging in duration from 8 to 24 months. We have made no attempt to explain the mechanism of recovery. Whether the beneficial ef-

fects are due to the specific action of the serum or not, is beyond the purpose of this report. We are merely presenting five proved cases of undulant fever which apparently recovered, following the administration of a specific polyvalent serum.

We wish to express our appreciation to Dr. L. J. Wenger of the Sharp and Dohme laboratories for his help in this study.

BIBLIOGRAPHY

- 1 Personal communication from the Division of Sanitary Reports and Statistics, United States Public Health Service
- 2 CARPENTER, C. M., and BOAK, R. A. The treatment of human brucellosis: a review of current therapeutic methods, *Medicine*, 1936, xv, 103-127

DETERMINATION OF THE NORMAL CIRCULATION TIME FROM THE ANTECUBITAL VEINS TO THE PULMONARY CAPILLARIES BY A NEW TECHNIC ¹

By SAMUEL CANDEL, M D , *Brooklyn, New York*

IN the original determinations on the velocity of blood flow in man by Blumgart and Weiss,¹ a method was employed in which radium was injected. This required an elaborate apparatus for the detection of radium and did not lend itself to wide clinical use, so that in later studies, simpler methods were devised.

The vast majority of the tests now practiced have for their starting point the injection of some substance into a vein in the antecubital fossa. The time that it takes that substance to move in the blood stream to another fixed point is measured. Depending upon the method used, the circulation time through one or the other of two pathways is determined. One ends in the pulmonary capillaries and includes the venous channels from the antecubital fossa through the superior vena cava to the right auricle, the right ventricle and the pulmonary artery. The other ends in capillaries which are the terminal branches of a systemic arteriole and includes the venous channels leading from the antecubital fossa through the superior vena cava to the right auricle, the right ventricle, the pulmonary artery, the pulmonary capillaries, the pulmonary vein, the left auricle, the left ventricle and the aorta.

The measurement of the first pathway includes only the right heart and gives us what is known as the "pulmonary circulation time." The measurement of the second circuit is spoken of as the "complete circulation time" and includes both the right heart and the left heart. In this paper we shall deal only with a method for measuring the pulmonary circulation time.

The methods which are now commonly employed to measure the pulmonary circulation time consist in the injection into one of the antecubital veins of a volatile substance such as ether,^{2, 3} perfumes, guaiacol, sodium cacodylate, allyl sulphide, methyl salicylate,³ colloidal sulphur.⁴ The time it takes for the appearance of their characteristic odors on the breath is measured. The test may be used either subjectively by instructing the patient to signal immediately on perceiving the odor, or objectively, by the observer himself smelling the drug.

The methods which have been just described have the following disadvantages

* Received for publication July 24, 1937

From the Medical Service of Dr. M. A. Rabinowitz

1 If the patient is required to notify the operator when he perceives the odor, then the method shares the disadvantages common to all subjective methods

2 If the operator relies upon his own sense of smell, the method still has the disadvantage that the sense of smell in man is the most poorly developed of all his faculties

Several years ago, Dr Charles H. Birnberg⁵ of the Department of Obstetrics, in attempting to produce amnesia during labor by the intravenous administration of paraldehyde, noticed that practically all patients would cough before the needle was removed from the vein. When this observation was described to the present investigator, the possibility occurred to him of making this the basis of a new method for the determination of the pulmonary circulation time.

A perusal of the literature revealed that Noel and Souttar⁶ were apparently the first to use paraldehyde intravenously as a hypnotic. They observed that in five seconds the patient tasted paraldehyde. In ten seconds the patient had a sensation of dizziness. It is significant that the authors used paraldehyde and found it a safe hypnotic even in grave cardiac and pulmonary disease.

Honan and Hassler⁷ administered a mixture of ether and paraldehyde intravenously for anesthesia. They reported excellent results but discontinued their use because the drugs were rapidly eliminated from the lungs and seemed to produce a decided irritation of the larynx.

Collier⁸ used a mixture of paraldehyde and ether intravenously as an anesthetic, and in four cases observed that paraldehyde appeared on the breath 30, 10, 15, and 10 seconds, respectively, after the injection.

Nitzescu and Iacobovici⁹ utilized paraldehyde in an isotonic solution of glucose for basal anesthesia. They reported 82 cases with satisfactory results aside from the disagreeable odor on the breath.

Johnson¹⁰ gave 5 c.c. of paraldehyde intravenously. The patient lost consciousness in 10 seconds and coincidentally with the onset of anesthesia, the patient coughed and a strong smell of paraldehyde was noted on the breath. He found the drug satisfactory because it was stable, easy to procure, required no sterilization and had a wide margin of safety.

Beauchemin et al.¹¹ induced general anesthesia in 55 patients. Their average dose was 9.2 c.c. for an adult weighing 60 kilograms. Nineteen cubic centimeters, the largest dose used, was given to an individual weighing only 46 kilograms. They noticed that a cough occurred during the injection and discussed a method of administration devised to decrease the cough.

Since paraldehyde is excreted in the lungs and produces a cough, can readily be procured, requires no sterilization, and since relatively large amounts can be injected without harmful effect, we did not hesitate to apply

its intravenous injection in order to develop an objective method* for the determination of the pulmonary circulation time

I have found that 1.4 c.c. (an amount about one-sixth as large as the average therapeutic dose for anesthesia) is the minimum volume of paraldehyde which when given intravenously produces a cough reflex most consistently. In some individuals, 0.8 c.c. and in one patient, 0.2 c.c. was sufficient. Therefore, in practically every case, 1.4 c.c. of paraldehyde (U.S.P.) was the dose used. The time which elapsed between the moment of injection and the appearance of the cough was measured with a stopwatch.

One hundred males and females, with apparently normal cardio-vascular systems, varying in age from 15 to 70 years were tested by this method. The results of these tests are summarized in table 1. The injections were given through a large bore needle (18 gauge) so that no time would be lost on account of mechanical resistance to the introduction of the drug.

TABLE I

* Blood Velocity in 100 Patients with Apparently Normal Cardiovascular Systems

AGES OF PATIENTS	Pulmonary Circulation Time in Seconds *				TOTALS
	3-4.5	5-6.5	7-8.5	9 or more	
61 years and over	1	3	3	0	7
46-60 years	3	11	4	3	21
31-45 years	6	19	4	3	32
15-30 years	3	25	9	3	40
TOTALS	13	58	20	9	100

* Corrected to nearest half second

A cough reflex was obtained in 96 per cent of the cases where 1.4 c.c. of paraldehyde was used. The cough paroxysm lasted from a few seconds to 2 or 3 minutes. Two of the patients fell asleep for a few minutes, after the injection of the drug. When they awoke they had no unpleasant after-effects. Most of the other patients complained of a sensation of dizziness, but this wore off quickly. Another complication, which occurred in three cases, was venous thrombosis. However, there was no sloughing of tissue or other harmful result.

As has just been mentioned, no cough reflex was produced in four instances. In these, however, when the test was repeated after 15 minutes,

* It may be mentioned that the test may be modified and used as a subjective one, utilizing a smaller dose of paraldehyde. The end point would then be given by the patient signalling in some way that he has smelled the drug.

a cough reflex was obtained. In such cases, or where too small amounts are injected to produce a cough reflex, one can use as an end-point, a sudden marked change in facial expression when the patient begins to smell the obnoxious substance.

Since the possibility existed that the circulation time had some correlation with the age of the patient, the results of the present study are classified according to the age of the patient (table 1). However, the various groups in table 1 are too small in numbers to permit the calculation of any correlation which might or might not exist. Therefore, the table has been condensed into 9 groups of patients to form table 2 and the distribution of the various circulation times was calculated for each age group.

TABLE II
Relation between Age of Patient and Pulmonary Circulation Time

AGES OF PATIENTS		Pulmonary Circulation Time in Seconds			TOTALS
		3-4 5	5-6 5	7-10 5	
46 years or over	No cases Per cent	4 0 14 ± 04*	14 0 50 ± 06	10 0 36 ± 06	28 100
31-45 years	No cases Per cent	6 0 19 ± 05	19 0 59 ± 05	7 0 22 ± 05	32 100
15-30 years	No cases Per cent	3 0 07 ± 03	25 0 63 ± 05	12 0 30 ± 05	40 100
	Total Per cent	13 0 13 ± 02	58 0 58 ± 03	29 0 29 ± 02	100 100

* In this paper, the figure following the \pm sign denotes the probable error. The probable error = $\pm 0.6745 \sqrt{\frac{P(1-P)}{N}}$

P = frequency in per cent
 N = Total number of cases

In addition to the frequency, the probable error of each frequency was calculated. It is apparent almost on inspection that there is no significant difference in the circulation time in different age groups. For example, let us take an apparently extreme difference, namely, between the frequency of occurrence of a short circulation time (column 1) in the age groups, 15 to 30 years and 31 to 45 years. In the former group, the frequency is 7 per cent and in the latter 19 per cent, so that the difference between the two frequencies is 12 per cent.

The probable error of a difference = $\sqrt{P_1^2 + P_2^2}$ where P_1 and P_2 are the probable errors of the two observed frequencies, which are being compared, provided that the observed frequencies are independent of one another, as in the present instance. Hence, the probable error of the difference in question = $\sqrt{(0.07)^2 + (0.19)^2} = \sqrt{0.034} = 0.6$ or 6 per cent. Hence,

even this apparently extreme difference (12 per cent) is less than 3 times its probable error. From this we may conclude that there is no correlation between age and circulation time.

Since there is no correlation between age and the pulmonary circulation time, it is permissible to combine all the observations when calculating the normal range (table 3).

TABLE III
Calculation of Mean and Standard Deviation

P C T *	f	x	fx	x ²	fx ²
30	3	-30	-90	90	270
35	2	-25	-50	625	1250
40	4	-20	-80	40	160
45	4	-15	-60	225	90
50	24	-10	-240	10	240
55	10	-05	-50	025	25
Arbitrary Mean 60	19	00	00	00	00
65	5	+05	+25	025	125
70	11	+10	+110	10	110
75	2	+15	+30	225	45
80	5	+20	+100	40	200
85	2	+25	+50	625	125
90	4	+30	+120	90	360
95	0	+35	+00	1225	00
100	4	+40	+160	1600	640
105	1	+45	+45	2025	2025
TOTALS	100		+70		2605

* Pulmonary circulation time corrected to nearest half second

f = absolute frequency of occurrence

x = deviation from the arbitrary mean

$$\text{Arbitrary Mean} = 60$$

$$\text{True Mean} = \text{Arbitrary Mean} + \frac{\sum fx}{\sum f}$$

$$= 6 + \frac{7}{100}$$

$$= 6.07 \text{ seconds}$$

$$\text{Standard Deviation} = \sqrt{\frac{\sum fx^2}{\sum f} - \delta^2}$$

$$= \sqrt{\frac{2605}{100} - (0.07)^2}$$

$$= 1.61$$

(δ = Difference between arbitrary and true means)

Thus, it may be seen that the mean pulmonary circulation time, by the author's method, is 6.07 seconds and the standard deviation about the mean

is 1.61 seconds The probable error of the mean

$$= \pm 0.6745 \frac{\text{Standard Deviation}}{\sqrt{N}},$$

where N = number of patients tested

$$= \pm 0.6745 \frac{1.61}{\sqrt{100}}$$

$$= \pm 0.11 \text{ seconds}$$

The probable error of the standard deviation

$$= \pm 0.6745 \frac{\text{Standard Deviation}}{\sqrt{2N}}$$

$$= \pm 0.08$$

Summarizing, Mean = 6.07 ± 0.11 seconds

Standard Deviation = 1.61 ± 0.08 seconds

Since 95 per cent of all random observations will fall between the limits of 2 times the standard deviation added to and subtracted from the mean, we may take the normal range as 2.8 to 9.3 seconds. When a determination falls outside of this range the odds against its being normal are 20 to 1. Since 99.7 per cent of the normal observations will fall within the range, mean ± 3 times the standard deviation, if a pulmonary circulation time greater than 11 seconds is encountered, the odds are approximately 300 to 1 that the finding is abnormal.

DISCUSSION

The average pulmonary circulation time as determined by Hitzig² was 4 to 8 seconds. The average time obtained by Miller³ was 6 to 9 seconds though there were occasional determinations as low as 3.5 seconds and others as high as 11.5 seconds.

In our series, the calculated mean was approximately 6 seconds. The normal range may be taken as about 3 to 9.5 seconds. A finding over 11.0 seconds can safely be considered abnormal since the odds are 300 to 1 against its being normal.

The method of determining circulation time by using paraldehyde has the following advantages:

- (1) The end point, a sharp cough, is purely objective.
- (2) The drug has a wide margin of safety.
- (3) The drug is readily available and may be taken directly from the bottle without previous preparation or sterilization.

The disadvantages of the use of paraldehyde are:

- (1) It causes a transitory dizziness which, however, passes away in several minutes.

(2) Rarely, in the doses used, it may cause complete hypnosis lasting a few minutes. However, there were no unpleasant after-effects when the patient recovered from the hypnosis.

(3) The cough usually lasts from 1 to 3 minutes. It may be paroxysmal and hard. Theoretically, it might seem unwise to produce a cough paroxysm in a cardiac patient for whom the test would most frequently be indicated. Actually, in a series of such patients, now being studied, the cough has resulted in no untoward symptoms.

(4) Venous thrombosis may occasionally result, but the frequency of this complication is much lower than with other drugs that have been used.

CONCLUSIONS

1 A new method for the determination of the pulmonary circulation time is described.

2 1.4 c.c. of paraldehyde, intravenously, was the dose used.

3 A cough reflex was obtained in 96 per cent of cases at the first attempt. In the other 4 per cent, a cough was produced upon repeating the test.

4 There is no correlation between the age groups studied and the pulmonary circulation time.

5 The mean value of the pulmonary circulation time in 100 adult male and female patients with apparently normal cardio-vascular systems was approximately 6 seconds. The normal limits are 3 and 9.5 seconds.

6 A finding of a pulmonary circulation time over 11.0 seconds is almost certainly abnormal.

I wish to express my deep gratitude to Dr Meyer A. Rabinowitz for his inspiration and constant encouragement which has always marked the relationship of the master to his pupils.

I am greatly indebted to Dr A. S. Wiener of the Department of Genetics and Biometrics of the Jewish Hospital for his invaluable aid in the statistical analysis.

I also wish to thank the services of Dr Louria and Dr Sussman from which some of the cases used in the present study were taken.

BIBLIOGRAPHY

- 1 BLUMGART, H. L., and WEISS, S. Studies on velocity of blood flow, method of collecting the active deposit of radium and its preparation for intravenous injection, *Jr Clin Invest*, 1927, iv, 389-398.
- 2 HITZIG, W. M. Measurement of the circulation time from the antecubital veins to the pulmonary capillaries, *Proc Soc Exper Biol and Med*, 1934, 935-938.
- 3 MILLER, H. R. Velocity of blood flow in part of the pulmonary circulation, *Proc Soc Exper Biol and Med*, 1934, 942-944.
- 4 MICHALOVER, S. Personal Communication.
- 5 BIRNBERG, C. H. Personal Communication.
- 6 NOEL, H., and SOUTTAR, H. S. The anesthetic effects of the intravenous injection of paraldehyde, *Ann Surg*, 1913, lvi, 64-67, *Lancet*, 1912, 818.
- 7 HONAN, W. F., and HASSLER, J. W. Intravenous anesthesia, *Ann Surg*, 1913, lviii, 900-926.

- 8 COLLIER, G K Intravenous use of paraldehyde, New York State Jr Med, 1914, \iv, 130
- 9 NITZESCU, I I, and IACOBOVICI, I Nouveau procede d'anesthesie generale, anesthesie de base par injection intraveineuse de paraldehyde glucosee, Presse Med, 1934, xlii, 331-333
- 10 JOHNSON, A S The parenteral administration of paraldehyde for the control of pain and convulsive states, New England Jr Med, 1934, xxi, 1065-1067
- 11 BEAUCHEMIN, J A, SPRINGER, R G, and ELLIOTT, G A Intravenous anesthesia, Med Times and Long Island Med Jr, 1935, lxi, 179-184

THE VALUE OF SULFANILAMIDE IN THE TREATMENT OF INFECTIONS OF BLADDER AND UPPER URINARY TRACT; REPORT OF STUDY OF TWENTY-FIVE PATIENTS

By WILLIAM J. EZICKSON, A B, M D, *Philadelphia, Pennsylvania*

FOLLOWING the epochal work of Domagk,¹ wherein he used with success the original Prontosil, in the treatment of streptococcic infections, many investigators abroad reported their findings with the use of this drug. Scherber,² Anselm,³ Kramer,⁴ and others reported excellent results from its administration in clinical cases of puerperal fever, erysipelas, etc. Following this Colebrook and Kenny⁵ proved its value in the treatment of puerperal infection due to hemolytic streptococci. The first American report was made by Long and Bliss,⁶ in which they corroborated experimentally and clinically the work done abroad. All this earlier work showing the value of the original prontosil and of sulfanilamide in the treatment of infection due to streptococcus has been corroborated and greatly extended since.

The value of sulfanilamide in the treatment of infections other than those due to the streptococcus was early reported. Buttle, Gray and Stevenson,⁷ and Proom⁸ showed its usefulness in meningococcic infections, Cooper, Gross and Mellon,⁹ and Rosenthal¹⁰ in type III pneumococcic infections and Dees and Colston,¹¹ in gonococcic infections.

After very careful study the Council on Pharmacy and Chemistry of the American Medical Association¹² voted to accept sulfanilamide for inclusion in New and Non-Official Remedies as a therapeutic agent for the treatment of infections by hemolytic streptococci of Lancefield's serologic group A (May 29, 1937).

CLINICAL INVESTIGATION

A group of 25 patients, having various types of infections of the bladder and upper urinary tract, were studied and treated with sulfanilamide. This group included for the most part, patients who have been under our care for a period of several months to several years, for infections of kidney and bladder, and who failed to respond to any previous treatment.

This study included the following data: (1) Age, (2) Sex, (3) Previous history, (4) Present diagnosis, (5) Symptoms before treatment, (6) Duration of symptoms, (7) Appearance of urine before treatment, (8) Culture of urine before treatment, (9) Total number of days treated, (10) Improvement noted (number of days after treatment was instituted), (11) Symptoms after treatment, (12) Appearance of urine after treatment.

* Received for publication November 27, 1937.

From the Calculus Research and Urologic Clinics, Department of Urology, Pennsylvania Hospital, Philadelphia, Pa.

(13) Culture of urine after treatment, (14) Average pH of urine during treatment, (15) Reaction, (16) Present condition

The accompanying table briefly summarizes these data (table 1)

Age The age groups were as follows

Between 20 and 30	1
" 30 and 40	5
" 40 and 50	9
" 50 and 60	6
" 60 and 70	1
over 70	3

Sex Twenty-one males and four females were studied and treated

Previous History One patient (case 3) had a left nephrectomy in 1927 for renal tuberculosis and also a bilateral epididymectomy (tuberculosis) in 1929. Four patients (cases 7, 8, 11 and 15) had urethral strictures, one of which (case 15) was complicated with a perineal fistula and an external perineal urethrotomy was done. Six patients (cases 6, 9, 12, 14, 24 and 25) had a transurethral prostatic resection. The length of time elapsing from the time of operation until present treatment was from three weeks to three years. Seven patients (cases 1, 16, 17, 18, 19, 20 and 21) had renal or ureteral calculi or both, with renal or bladder infection. Three of these had a ureterolithotomy, one had a pyelolithotomy, one a nephrolithotomy, one had a nephrectomy and one had two pyelolithotomies and a nephrectomy. Two patients (cases 2 and 4) had several attacks of pyelonephritis over a period of several years. Two patients (cases 5 and 10) had symptoms of prostatism with chronic myocarditis and arteriosclerosis. One patient (case 22) had a perineal prostatectomy. One patient (case 13) had a suprapubic prostatectomy in 1935, a transurethral resection of contracted vesico-urethral orifice in 1936 and this was followed by incontinence of urine, which condition still exists. One patient (case 23) had chronic prostatitis and cystitis.

Present Diagnosis—Cystitis. Nine patients (cases 4, 6, 9, 12, 13, 14, 22, 24 and 25).

Pyelonephritis. Four patients (cases 16, 17, 19, 21).

Urethral stricture and cystitis. Three patients (cases 7, 11, 15).

Prostatic hypertrophy with cystitis. Two patients (cases 5 and 10).

Prostatitis and cystitis. Two patients (cases 8 and 23).

Calculus pyonephrosis and cystitis. Two patients (cases 1 and 18).

Pyelonephritis and cystitis. Two patients (cases 2 and 20).

Renal and bladder tuberculosis with mixed infection. One patient (case 3).

Symptoms before Treatment Most of the patients (18 cases) had the following symptoms: Frequency, diurnal and nocturnal, urgency and dysuria. Several in this group also had hematuria. The others (7 cases) had lumbar pain and some dysuria.

Duration of Symptoms This varied from several months to five years. Ten of these patients had symptoms from one to two years, nine from two to five years and only six under one year.

Appearance of Urine before Treatment The urine before treatment was cloudy in all but two instances, and in these it was hazy.

Cultures of Urine before Treatment The *B. coli* was found in the cultures of the urine before treatment in eleven of the cases. In two instances culture revealed *B. pyocyaneus* and *B. coli*, in two cases, Friedlander's bacillus, in one case *Staphylococcus albus*, in one case *Staphylococcus albus hemolyticus* and non-hemolytic streptococcus, in one case, a pure culture of hemolytic streptococci, in one case *Staphylococcus albus hemolyticus* and hemolytic streptococci, in one case non-hemolytic *Staphylococcus albus*, in one case an unidentified gram positive micrococcus, in one case there was no growth in 72 hours.

Total Number of Days Treated Treatment was carried out for from one to eleven weeks. Most of the patients (14 cases) were not treated for more than four weeks. Only two were continued on treatment for more than eight weeks.

Improvement Noted (Number of days after treatment was instituted) Sixteen patients showed improvement, symptomatic or clearing of the urine or both, within one week. Two showed improvement in 10 days, two in two weeks, one in three weeks and four showed no improvement at any time. Two of the 16 patients who showed improvement within one week continued this improvement for a period of about four to six weeks and then all the original symptoms returned in as severe a form as before treatment was started.

Symptoms after Treatment Most of the patients (18 cases) had the following symptoms before treatment: frequency, urgency, dysuria and nocturia. In every instance but three, these symptoms disappeared entirely or were diminished in severity after from one to two weeks' treatment. The most persistent symptom was nocturia but in most instances the number of voidings at night was much decreased.

Appearance of Urine after Treatment The urine became clear in 15 cases. The appearance improved from cloudy to hazy in six cases and there was no improvement in the cloudiness of urine in four cases.

Culture of Urine after Treatment In nine cases a negative culture of the urine was obtained after one to four weeks of treatment. The organisms found in this group before treatment were chiefly the *B. coli* and the streptococcus. In the remaining 16 cases a wide variety of results were obtained. In two patients who had both renal and bladder infection (*B. coli*) a negative culture was obtained from the involved kidney but the *B. coli* was still found in the bladder urine. No change occurred in the cases in which we had found the *B. proteus*, Friedlander's bacillus or the *B. pyocyaneus*, before treatment. In several of the cases in which we obtained

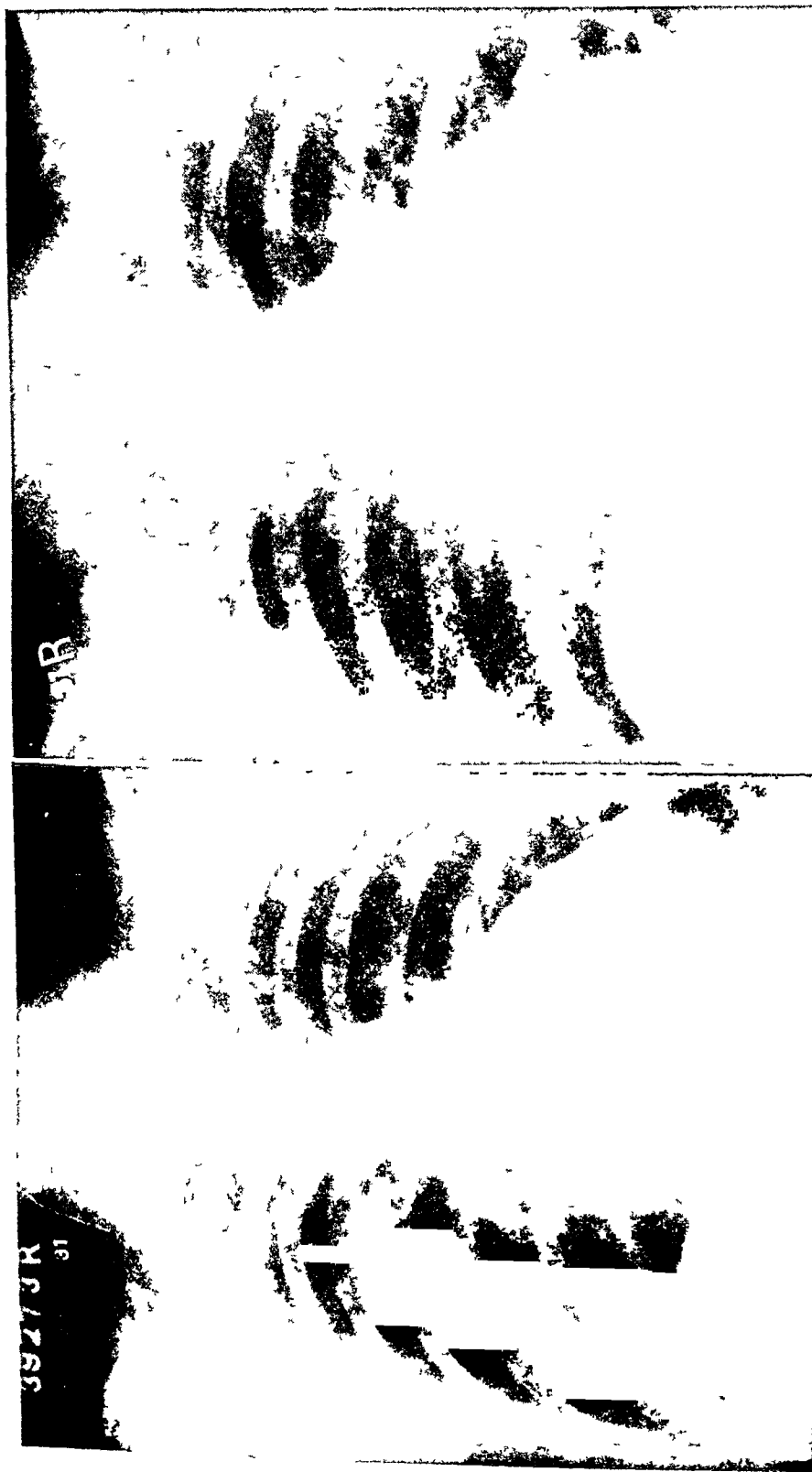


Fig 1 a Roentgenogram of chest, taken two months after the onset of symptoms, indicates a generalized cardiac enlargement

Fig 1 b A progressive enlargement of the heart is noted in this roentgenogram, taken one month later

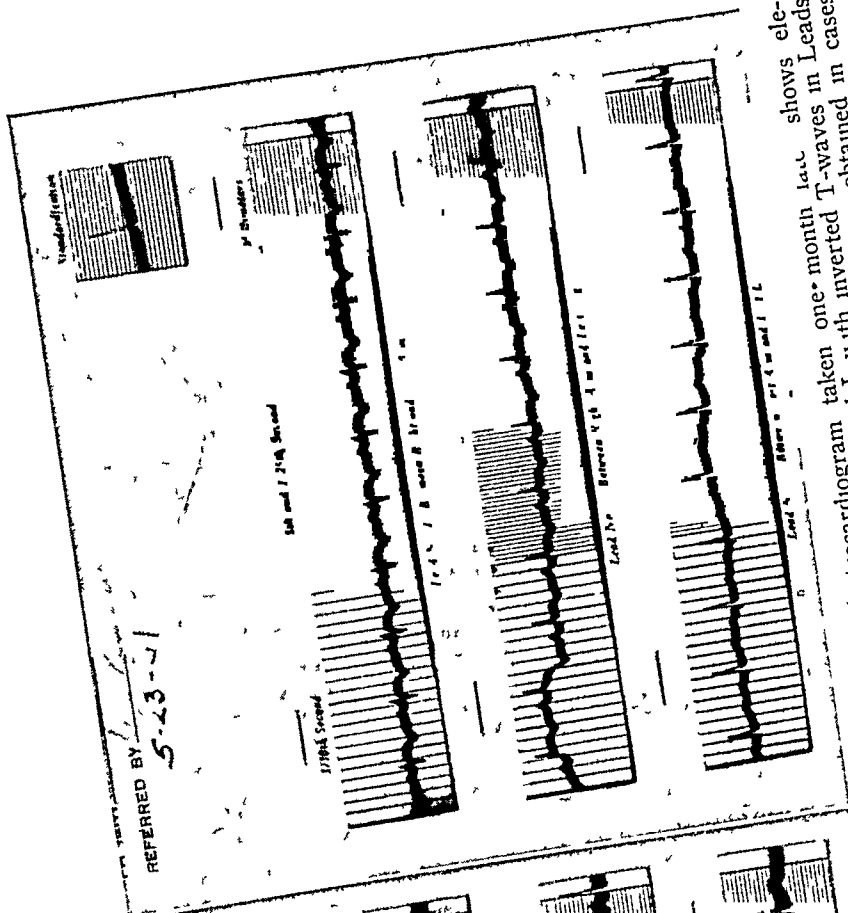


FIG 2b Electrocardiogram taken one month later shows elevation of the ST intervals in Lead I, with inverted T-waves in Leads I and II, closely simulating the electrocardiograms obtained in cases of recent coronary thrombosis



FIG 2a Electrocardiogram on April 24 shows beginning inversion of the T-waves, with moderate upward convexity of ST intervals in Lead I. Auricular extrasystoles are present

The patient died on June 16, 1931

Necropsy Findings The necropsy was performed by Dr G. L. Berdez, pathologist at St Mary's Hospital, and the following is based on his report

The body measured 172 cm in length and was in a moderately good state of nutrition. There was a marked edema of the legs, thighs and of the external genitalia, as well as a moderate distention of the abdomen.

On opening the thorax it was noted that the cavity of the pericardium was completely obliterated by grayish-white tumor masses, which glued together the visceral



FIG 3 Photograph of gross specimen shows the extensive involvement of the visceral and parietal pericardium

and parietal layers of the pericardium. It was with difficulty that the pericardial adhesions could be separated, and most of the tumor masses remained attached to the epicardium (figure 3). These tumor masses were very hard and measured up to 1 cm in thickness, and in places infiltrated the more superficial layers of the myocardium. They were grayish-white, friable, and showed areas of necrosis. Almost the entire surface of the visceral and parietal layers of the pericardium was covered with the tumor tissue, which also completely surrounded the base of the aorta and the first part of the pulmonary artery, rendering them quite rigid. The mitral and tricuspid valves were patent for two fingers, the aortic and pulmonary valves were com-

petent There were a few yellowish spots on the mitral valves, but no further deposits were noted on the valves or on the endocardium The myocardium was brownish red and somewhat edematous The heart weighed 800 gm Several small lymph glands around the arch of the aorta were found to be extensively invaded by the tumor tissue

The right pleural cavity contained 2,000 c c of clear serous fluid, and no adhesions were noted, while the left pleural cavity contained 1,000 c c of clear serous

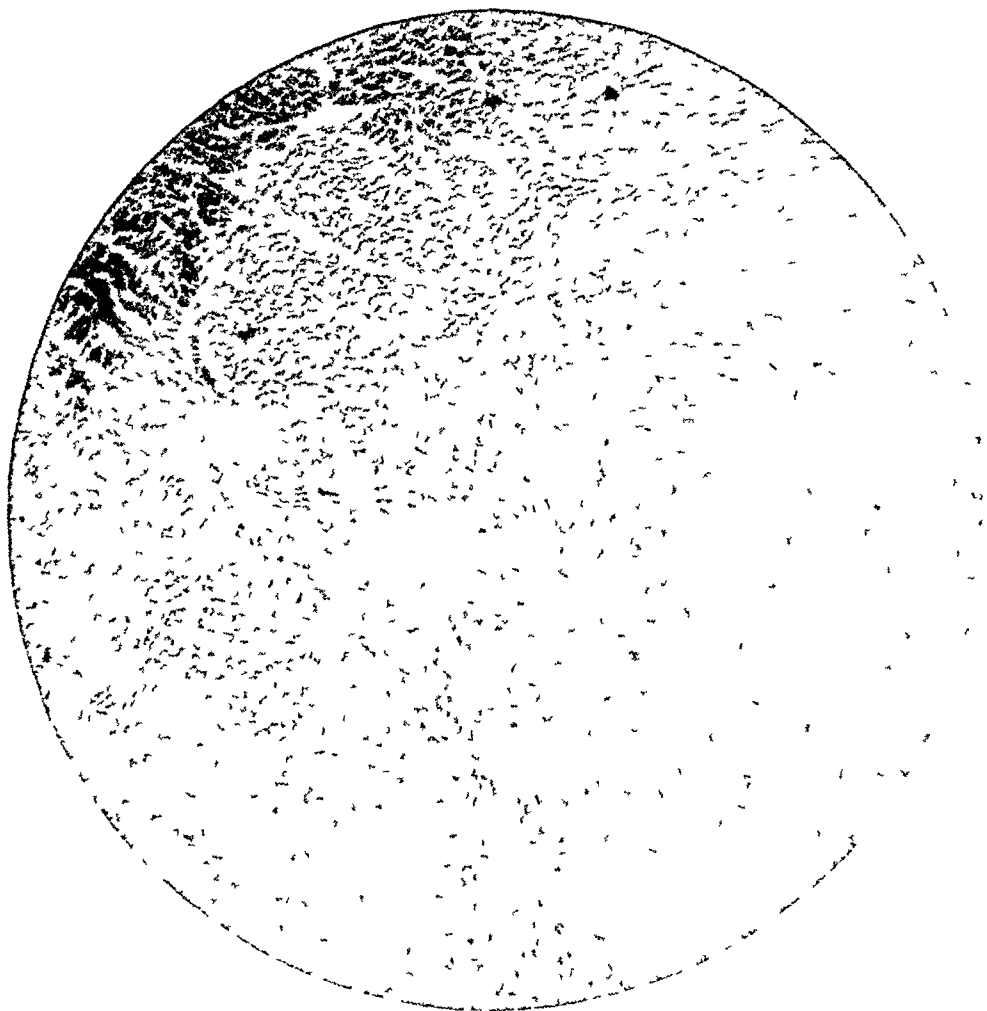


FIG 4 Photomicrograph of the pericardium—low power magnification

fluid, and several fibrous adhesions were noted over the upper left lobe The right and left lungs weighed respectively 325 and 430 gm A large hemorrhagic infarct was noted in the lower left lobe, and in the corresponding branch of the pulmonary artery was a moderately large embolus

The lung tissue as a whole was congested and edematous No evidence of metastatic invasion was noted in the lungs, in the peribronchial or tracheal lymph glands

The abdominal viscera were essentially negative except for evidence of chronic congestion (No evidence of metastatic malignancy was found)

Microscopic examination of the tumor masses (figures 4 and 5) of the pericardium showed that the tumor tissue was formed by spindle cells which infiltrated diffusely the tissue of the pericardium, including the subserous layers. In certain areas the tumor tissue extended to the superficial layers of the myocardium. Small round spaces could be recognized here and there in the tumor tissue, representing

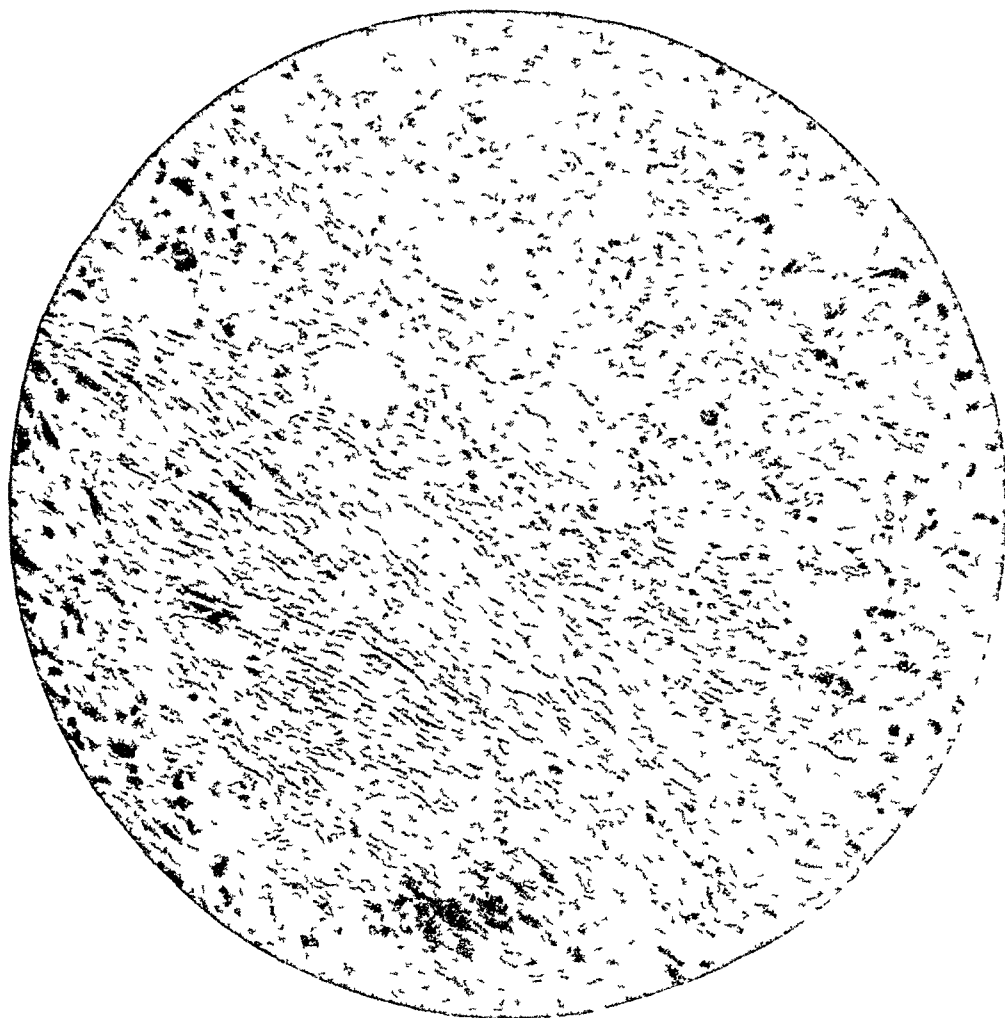


FIG 5 Photomicrograph of pericardium

what was left of the adipose tissue of the subepicardial layers. The tumor cells were arranged in bundles, pointing in various directions, and large areas of tumor tissue were completely necrotic. The tumor cells showed a marked irregularity in shape and size and contained nuclei which were generally elongated, moderately rich in chromatin, occasionally multiple, and at times showing mitotic figures. In certain sections groups of tumor cells filled the smaller veins and lymphatics, and in the myocardium adjacent to the tumor tissue areas of lymphocytic infiltration were noted.

The lymph glands located at the arch of the aorta showed extensive replacement by tumor tissue having a structure similar to that noted in the pericardium

A diagnosis of spindle cell sarcoma of the pericardium was made by Dr Berdez

COMMENT

The necropsy findings indicate a case of primary sarcoma of the pericardium, involving extensively the visceral and parietal pericardium to the extent that the pericardial cavity was entirely obliterated by a fusion of the tumor masses. There was only a moderate invasion of the myocardium, and the only evidence of metastatic invasion was found in the small lymph glands around the arch of the aorta. The physical and roentgen findings supported a diagnosis of pericarditis, and gave no clue as to the true etiological factor underlying the disease process. The electrocardiographic records are of considerable interest in that they closely resembled the electrocardiographic records obtained in cases of recent coronary thrombosis. They showed the presence of progressing myocardial disease, but nothing which could be considered characteristic or diagnostic of a malignant condition. It is the opinion of several authors (Willius and Amberg,⁶ Siegel and Young,⁷ Houck and Bennett⁸), that electrocardiograms in primary or secondary tumors of the heart do not show any findings which are characteristic of the malignant conditions but rather simulate the electrocardiographic findings associated with myocardial changes from other causes.

CONCLUSIONS

A case of primary sarcoma of the pericardium with physical, roentgenographic, electrocardiographic and necropsy findings has been presented, to be added to the relatively small number of cases previously reported.

BIBLIOGRAPHY

- 1 YATER, W M Tumors of the heart and pericardium, pathology, symptomatology and report of nine cases, Arch Int Med, xlviii, 627-666
- 2 LYMBURNER, R M Tumours of heart histopathological and clinical study, Canadian Med Assoc Jr, 1934, xxx, 368-373
- 3 PERLSTEIN, I Sarcoma of the heart, Am Jr Med Sci, 1918, cli, 214
- 4 MORRIS, J J Primary sarcoma of heart, Jr Lab and Clin Med, 1933, lviii, 935-940
- 5 BARNES, A R, BEAVER, D C, SNELL, A M Primary sarcoma of the heart, report of case, with electrocardiographic and pathologic studies, Am Heart Jr, 1931, iv, 480-491
- 6 WILLIUS, F A, and AMBERG, S Two cases of secondary tumor of heart in children, in one of which diagnosis was made during life, Med Clin N Am, 1930, xiii, 1307-1316
- 7 SIEGEL, M L, and YOUNG, A M Electrocardiographic findings in tumors of the heart, Am Heart Jr, 1933, viii, 682
- 8 HOUCK, G H, and BENNETT, G A Polypoid fibroma of left auricle (so-called cardiac myxoma) causing ball valve action, with report of case, Am Heart Jr, 1930, v, 787-794

EDITORIALS

THE EXPERIMENTAL PRODUCTION OF HYPERTENSION

THE question of the etiology of chronic renal disease and of the cardiovascular lesions commonly associated with it has long interested investigators, and many attempts have been made to reproduce these conditions in animals. Although some of these efforts have met with a measure of success, hitherto the experimental disease has never closely duplicated that seen in man. An important advance toward a solution of some phases of this problem has recently been accomplished through the work of Goldblatt and his associates.¹

These investigators were the first to reproduce in animals a condition closely resembling essential hypertension in man. This they accomplished in dogs, and later in monkeys, by producing renal ischemia by partially clamping off one or both main renal arteries. They were able to control the severity of the disease produced by varying the degree to which the arteries were constricted. By causing moderate obstruction of one or both arteries, a sustained benign type of hypertension was produced. In animals in which only one artery was partly obstructed, the hypertension tended to subside after varying intervals, whereas in others in which both renal arteries were so treated, it persisted indefinitely, in some animals for more than five years. These animals usually showed no evidence of impairment of renal function by the ordinary clinical tests and seemed normal in other respects. No detailed description of the lesions found in these animals has yet been published, but thickening of the media and thickening and hyalinization of the intima of the retinal and other systemic arterioles are mentioned.

If the ischemia was relieved by releasing the clamp, the hypertension promptly subsided. The hypertension could not be prevented or relieved by such procedures as bilateral sympathectomy, or section of the anterior spinal nerve roots. If the ischemic kidney was removed, however, the blood pressure fell promptly to normal provided that the other kidney had not been injured. Removal of both kidneys or complete occlusion of all the renal vessels does not cause hypertension. Such facts led Goldblatt² to the conclusion that the hypertension must be due to the action of some humoral substance which is produced in the kidney tissue when damaged by ischemia. Nothing definite is yet known as to the nature of this "hypothetical effect substance," or as to the mechanism by which it produces the hypertension except that some adrenal cortex must be present.

¹ GOLDBLATT, H., LYNCH, J., HANZAL, R. F., and SUMMERVILLE, W. W. Studies on experimental hypertension. (I) The production of persistent elevation of systolic blood pressure by means of renal ischemia, *Jr Exper Med*, 1934, 11, 347.

² GOLDBLATT, H. Studies on experimental hypertension. (V) The pathogenesis of experimental hypertension due to renal ischemia, *ANN INT MED*, 1937, 11, 69.

More recently Goldblatt³ has reported the production of a malignant type of hypertension by more markedly constricting both renal arteries. These animals showed a very high blood pressure and quickly developed evidences of grave renal insufficiency with elevation of the non-protein nitrogen and creatinine in the blood. After varying intervals they became anuric, developed convulsions and coma and died in uremia. At necropsy the most striking findings consisted of numerous petechial hemorrhages caused by focal lesions in the capillaries and arterioles. The arterioles showed a deposition of hyalin beneath the intima and areas of necrosis. These lesions were regarded as identical, except for their greater severity, with those found in human cases of malignant hypertension. They were found in the systemic vessels in many areas, but not, however, in the kidneys. Their production apparently depends upon both the presence of a humoral toxic substance and a high tension within the vessels.

In some animals intermediate types of disease were produced—sustained hypertension with at first slight impairment of renal function, and later, perhaps after a long interval, grave renal insufficiency and death in uremia.

Much of Goldblatt's work has already been confirmed by other investigators⁴.

This work has an evident application only to certain phases of renal disease in man. It offers no obvious help in explaining the production of diffuse glomerular nephritis of infectious origin. If hypertension in man is also a result of renal ischemia, the site of the obstruction to the circulation must be in the small vessels, particularly the preglomerular arterioles. The fundamental cause of these arteriolar changes remains obscure. In spite of these limitations, however, such experiments provide new and promising methods of approach to many problems concerning hypertension, and they should help to rationalize the treatment of this serious condition.

P C

POSTMORTEM EXAMINATIONS

IN this issue Dr Alan Gregg has drawn attention to the value to the patient of demanding of his physician that a post mortem be performed in the event of his death. This highly original and valuable contribution to our thinking on this subject deserves wider circulation among the laity than it will receive through the pages of the *ANNALS*. The most effective method of spreading this doctrine would be for individual physicians to give to their patients a reprint of Dr Gregg's address to the College. With Dr Gregg's permission arrangements have been made therefore whereby any

³ GOLDBLATT, H. Studies on experimental hypertension (VII) The production of the malignant phase of hypertension, *Jr Exper Med*, 1938, 111, 809.

⁴ CHID, C G. Observations on the pathological changes following experimental hypertension produced by constriction of the renal artery, *Jr Exper Med*, 1938, 111, 521.

practicing physician can order such reprints direct from the Lancaster Press, Lancaster, Pennsylvania *

In the discussion of the pros and cons of State Medicine the present system of medical care is frequently attacked on the ground that it includes no method of supervision of the competency of the practitioner. Our position in this respect would be a stronger one if we could say that the quality of the medical care we offer cannot urgently need revision in the cases which have recovered, and that we advocate and work towards the goal of 100 per cent of autopsies of fatal cases as the best corrective of defects in our knowledge, skill or judgment.

* The cost may be computed by reference to the paragraph on Reprints on the back cover of this journal.

REVIEWS

The Therapeutic Problem in Bowel Obstruction By OWEN H WANGENSTEEN, M D, Ph D 360 pages, 17 × 25.5 cm Charles C Thomas, Springfield, Ill Price, \$6.00

This summary of the author's many investigations and experiences on the subject of intestinal obstruction is a small book of definite value. The practical utility of the book will be appreciated by the physician, the surgeon and the researcher. The bibliography contains generous quotations of more than one thousand authors.

Dr Wangenstein points out the "slender support by recent researches of the toxic theory" and demonstrates with persuasive eloquence the increasing evidence that mechanical factors are essential elements determining the mortality rate.

Therapeutics guided along these lines has reduced the mortality rate and "supports the denial of the fatality resulting from toxic absorption." At the same time, the suction method is not construed to be the choice of procedure in all cases of obstruction. "Operation still is and possibly will continue to be the chief mainstay of therapy in most forms of bowel obstruction. It is, however, apparent that some cases need not be operated upon, particularly patients with partial obstruction of the small intestine." Early operation is the choice in strangulation obstructions.

C F H

Pocket Atlas of Anatomy By VICTOR PAUCHET and S DUPRET 3rd edition 368 pages, 12 × 18.5 cm Oxford University Press, New York 1937 Price, \$4.00

Containing 345 plates and condensed to very convenient proportions this "Pocket Atlas of Anatomy" covers almost as much ground as its fellows of larger size. Although the plates are relatively small they are clear, detailed, well-labelled and not over-crowded. Each region is adequately dealt with and cross sections are included where important relations are to be demonstrated. There is no abbreviated text such as often detracts from the merits of other atlases. The terminology is that "adopted by the Anatomical Society at Birmingham in 1933, but where the names differ markedly from the Basle Nomina Anatomica, the B N A are retained in square brackets," which makes the book reasonably adaptable to all schools. The hope expressed on the fly-leaf that "this Pocket Atlas of Anatomy will be of service not only to students but to general practitioners and surgeons on account of its handiness and simplicity" has a fair chance of fulfillment if it is realized that books of its calibre are to be used in conjunction with textbooks and dissecting room study and not as a substitute for either.

M E

Clinical Roentgen Therapy Edited by ERNEST A POHLE, M D, Ph D, F A C R, Professor of Radiology, Chairman, Department of Radiology and Physical Therapy, University of Wisconsin, Madison, Wisconsin 819 pages, 15 × 24 cm Lea & Febiger, Philadelphia 1938 Price, \$10.00

This work constitutes an edition of chapters contributed by seventeen specialists of the United States, Canada, and Europe and represents the first real attempt to assemble the vast store of knowledge of roentgen therapy into a volume for the English speaking radiologists. Attempts to produce such a volume previous to this time have been fraught with discouragement due to the rapid changes that have been

taking place in this branch of medicine. With the standardization of the international "r" unit, the improvement of apparatus, the standardization of technics, and the ability to duplicate and check the results of investigators, the specialty of radiology has become more stabilized. A tremendous amount of material has been condensed by the authors who have maintained a keen sense of discrimination between that which is worthy and that which will not withstand the scrutiny of medical science. A multitude of conditions have been treated by the roentgen-rays and an honest effort has been made to evaluate the claims of over-enthusiastic workers.

The clinical aspect of many conditions considered has been included, a feature which makes for interest, completeness, and logic in comprehending the problems involved in the treatment of malignancy and infections. Controversies have not been included since details would defeat the purpose of the book. The extensive bibliography furnishes the reader with a supply of material for reference if he desires further information.

The editor uses occasional helpful foot-notes to explain, clarify, and correlate the writings of the foreign specialists with those of the American.

Because of the combined use of radium and roentgen-rays in certain conditions an adequate discussion of the use of the former is included in spite of the limitation suggested in the title. This volume can be recommended as an invaluable guide for every roentgenologist.

H J W

Clinical Urinalysis By ROBERT A. KILDUFFE, A.M., M.D., F.A.S.C.P. 428 pages, 23 × 14.5 cm. F. A. Davis, Philadelphia, Pa. 1937. Price, \$4.00.

This is a concise and comprehensive treatment of the subject of urinalysis intended for the use of the practicing physician. The text is well planned. There is a short history of the subject and a brief discussion of the anatomy and physiology of the kidneys. The major portion of the book is devoted to the composition of urine and the better methods of analysis available with interpretations of results. The author has also included an outline of equipment and reagents necessary for setting up an office laboratory. The book is not only of value to the physician who makes his own analyses but also to those who must interpret the reports from clinical laboratories.

E M R

Die physiologische und klinische Bedeutung des Blutammoniaks (Physiological and Clinical Significance of Blood Ammonia) By LAZAR STANOJEVIC, M.D. 64 pages, 16 × 23.5 cm. Theodor Steinkopff, Dresden and Leipzig. 1938. Price, RM 6.

This small monograph is essentially a critical survey of the literature (213 references) on the determination of the ammonia content of the blood and its significance in physiology, pathology and medicine. The author himself is an active investigator in this field. Workers engaged in research on this subject or individuals desiring detailed information on blood ammonia should find this book invaluable.

E G S

Practical Methods in Biochemistry By FREDERICK C. KOCH. Second edition. 302 pages, 16.5 × 23.5 cm. William Wood and Co., Baltimore. 1937. Price, \$2.25.

This laboratory manual is divided into three parts. Part I (74 pages) deals with experiments on carbohydrates, lipins, proteins and hydrogen-ion concentration, Part II (26 pages) describes experiments on salivary, gastric and intestinal digestion and Part III (124 pages) deals with qualitative and quantitative

experiments on blood and urine. Concise but adequate directions are given for 232 experiments.

"Although this manual is intended primarily as the practical companion to Professor Matthew's textbook, nevertheless it contains considerable explanatory matter," a feature which appeals particularly to the reviewer, "in order to help correlate the theoretical and laboratory aspects of the subject matter." Since over half of the experiments are devoted to blood and urine chemistry, the book should prove valuable not only to medical students but to hospital laboratory workers and clinical chemists as well. "However no attempt has been made to interpret the significance of the results in blood and urine analysis." Although the experiments and methods are well selected and clearly described, the reviewer feels that a few typical experiments on bio-colloid chemistry would be helpful additions to an otherwise valuable book. It is well printed and well bound and the subject matter is attractively presented to the eye by means of the variation in the size of the print. An index and adequate references to the original literature are included. A large and informative appendix (63 pages) containing an extensive list of reagents and solutions and detailed directions for their preparation, frequently including an exposition of the chemical principles involved, adds materially to the value of this laboratory manual.

E G S

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members

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- Dr Guy W Carlson, F A C P, Appleton, Wis—one reprint, "An Outbreak of Trichiniasis in East Central Wisconsin",
- Dr Norbert Enzer, F A C P, Milwaukee, Wis—one reprint, "Chronic Lung Changes in Electric Arc Welders",
- Dr A Allen Goldbloom, F A C P, New York, N Y—two reprints, "Schmincke's Tumor (Lympho-Epithelioma) with Metastases Complicated by Tracheo-Esophageal Fistula" and "Clinical Studies in Circulatory Adjustments IV Obliterating Pulmonary Arteritis with Secondary Pulmonary Changes and Right Ventricular Hypertrophy, Report of a Case with Autopsy",
- Dr Ernest E Hadley (Associate), Washington, D C—two reprints, "The Psychoanalytic Clarification of Personality Types" and "Unrecognized Antagonisms Complicating Business Enterprise",
- Dr Florimond J LeBlanc (Associate), Elgin, Ill—one reprint, "Oxidation Reduction in Colloidal Chemistry",
- Dr Lowell S Selling, F A C P, Detroit, Mich—two reprints, "The Endocrine Glands and the Sex Offender" and "Un Tipo Especial De Homosexualidad Encontrado En Las Escuelas Correccionales De Niñas"

SECTIONAL MEETING OF FLORIDA MEMBERS

Fellows and Associates of the American College of Physicians residing in Florida have organized an informal group for the purpose of closer acquaintanceship and a better opportunity to share each other's progress. They meet once each year on the day previous to the Florida State Medical Society meeting and in the same city. Fellows and Associates residing in or near the city in which the meeting is to be held have charge of the program, which consists of short clinical discourses in the forenoon, round table luncheon and a general visit and get-together in the afternoon. The organization is entirely informal, there being no by-laws and the expense is prorated by the members who attend each year.

The first meeting was held at Miami, May 9, 1938. Dr P B Welch, F A C P, Miami, was the first chairman and Dr Kenneth Phillips, F A C P, Miami, was the first secretary. Program was as follows:

- "Contagious Diseases of Childhood Immunization and Modification," Dr Warren Quillian, F A C P, Coral Gables,
- "Differential Diagnosis of Chest Pain," Clinic, Dr E Sterling Nichol, F A C P, Miami,
- "Modern Treatment in Diabetes Mellitus," Dr Arthur Walters (Associate), Miami Beach,
- "Advances in Fever Therapy by Physical Means," Motion Picture Demonstration, Dr Kenneth Phillips, F A C P, Miami

This was followed by a round table luncheon, there were fifty-five members in attendance.

MEETING OF PUERTO RICO MEMBERS

On June 12, 1938, Dr and Mrs R Rodriguez-Molina tendered a dinner party to the members of the American College of Physicians resident in Puerto Rico at their country home in Hato Tejas, Bayamon. The dinner was given in honor of Dr Ramon M Suarez, F A C P, Governor of the College for Puerto Rico. Dr Suarez gave a report to the members on the annual meeting of the College held in New York during April. The following were present:

Dr and Mrs R Rodriguez-Molina	Dr and Mrs Enrique Koppisch
Dr and Mrs Ramon M Suarez	Dr and Mrs Arturo Carrion
Dr and Mrs Cesar Dominguez	Miss Clemencia Benitez
Dr and Mrs Guillermo Marquez	Dr Antonio Ortiz
Dr and Mrs Juan Sabater	Dr Oscar Costa-Mandry
Dr and Mrs Luis Morales	

A delightful day was spent by all and matters pertaining to the College were amply discussed. Dr Suarez particularly recommended to all members of the College that they make arrangements to be present at the next Annual Session of the College, to be held in New Orleans, March 27 to 31, 1939.

Meetings of the Puerto Rico Chapter of the College have been primarily social occasions, due in part to the great number of medical meetings that are held locally. The Chapter feels the social gatherings better help than purely scientific meetings. In all the scientific meetings held by the various medical organizations in Puerto Rico, members of the College, comprising the Puerto Rico Chapter of the College, take active part.

O COSTA-MANDRY, F A C P

Dr Manfred Kraemer, F A C P, Newark, N J, was elected Chairman and Dr Hyman I Goldstein (Associate), Camden, was elected Secretary of the Section on Gastroenterology of the Medical Society of New Jersey, at its last annual meeting in Atlantic City during May.

Dr Thomas Kain, F A C P, Camden, and Dr John W Gray, F A C P, Newark, are Secretary and Chairman, respectively, of the Section on Medicine of this Society.

Dr Ralph E Porter (Associate), Superintendent of the U S Marine Hospital, Fort Stanton, N M, since 1934, has been appointed Superintendent of the Marine Hospital in Savannah, Ga.

Dr Henry A Christian, F A C P, and Dr Charles Sidney Burwell, F A C P, Boston, were among the chief speakers at the twenty-fifth anniversary celebration of the Peter Bent Brigham Hospital, Boston, May 5 to 7.

Dr Samuel M Feinberg, F A C P, Chicago, addressed the Clinton County (Iowa) Medical Society May 5 on "Summer Allergy."

Dr Andrew C Ivy, F A C P, Chicago, addressed the Genesee County (Michigan) Medical Society May 4 on "Clinical Aspect of the Physiology of the Gallbladder."

Dr Karl F Eschelman, F A C P , Buffalo, has been appointed consultant on firearms identification and ballistics to the Buffalo police department

Dr William J Mallory, F A C P , Washington, D C , addressed the Cambria County (Pa) Medical Society at Johnstown, June 9, on " Diagnosis and Management of the Common Diseases and Disturbances of the Digestive Tract "

Dr Thomas Parran, F A C P , Surgeon General of the U S Public Health Service, was a guest speaker at a symposium on syphilis before the Philadelphia (Pa) County Medical Society on May 11 Among the Philadelphia speakers were Dr Baldwin L Keyes, F A C P , and Dr Daniel J McCarthy, F A C P

Dr M Herbert Barker (Associate), Chicago, conducted a clinic on cardiovascular diseases and hypertension at the ninth annual meeting of the Ninth Councilor District Medical Society of Wisconsin, in Stevens Point, May 5

Dr Herman M Pollard (Associate) has been promoted to Assistant Professor of Internal Medicine on the faculty of the University of Michigan Medical School

The sixth annual assembly of the Omaha Mid-West Clinical Society will be held October 24 to 28, 1938, at the Hotel Paxton, Omaha Dr Henry L Bockus, F A C P , Philadelphia, and Dr O H Perry Pepper, F A C P , Philadelphia, will be guest speakers on the subject of medicine

Dr Arthur C Christie, F A C P , Washington, D C addressed the Medical Society of the County of Monroe (New York) May 17 on " Modern Trends in Medicine with Special Reference to Hospital Insurance "

Dr Max Pinner, F A C P , for some years principal diagnostic pathologist District Tuberculosis Hospitals, New York State Department of Health, has been appointed chief of the division of pulmonary diseases at Montefiore Hospital, New York City, beginning September 1

Dr Rufus I Cole, F A C P , was tendered a testimonial dinner at the Rockefeller Institute for Medical Research recently, at which he was presented with a bound set of reprints from the institute hospital, from which he resigned as director last year

Dr William Egbert Robertson, F A C P , Philadelphia, was recently appointed Medical Director of the Northeastern Hospital, Philadelphia

Dr B B Vincent Lyon, F A C P , has been made Associate Professor of Medicine at Jefferson Medical College of Philadelphia

Dr Edgar A Hines, F A C P , Seneca, has been re-elected secretary-treasurer of the South Carolina Medical Association

Dr John A Kolmer, F A C P, Philadelphia, addressed the Roanoke (Va) Academy of Medicine recently on "Infection, Immunity and Specific Treatment of Lobar Pneumonia"

The West Virginia State Medical Association held its seventy-first annual meeting at White Sulphur Springs July 11 to 13, under the presidency of Dr. Charles W Waddell, F A C P, Fairmont Dr Louis H Clerf, F A C P, Philadelphia, was among the guest speakers, his subject dealing with pulmonary suppuration Dr Charles B Chapman (Associate), Welch, delivered the oration on medicine, "Human Blood as a Therapeutic Agent"

Dr George H Gehrman, F A C P, Wilmington, Del, was a guest speaker at the meeting of the West Virginia Industrial Physicians and Surgeons Association, July 10, his subject being, "Industrial Medicine and Toxicology"

Dr William C MacCarty, F A C P, Rochester, Minn, addressed the Momoe County (Ind) Medical Society May 9 at Bloomington on "Cancer and Cancer Control"

Dr Elmer L Sevringhaus, F A C P, Madison, Wis, addressed the Shawnee County (Kan) Medical Society at Topeka on June 6, his subject being "Endocrine Therapy in General Practice"

Dr Daniel L Sexton, F A C P, St Louis, and Dr Euclid M Smith, F A C P, Hot Springs National Park, addressed the sixty-ninth annual meeting of the Southwestern Kentucky Medical Association at Paducah recently on "Endocrinology in General Practice" and "Management of the More Common Arthritic Disorders," respectively

Dr Maynard E Holmes, F A C P, has been promoted to Professor of Clinical Medicine at Syracuse University School of Medicine

Dr Wingate M Johnson, F A C P, Winston-Salem, has been elected President of the Board of Trustees of Wake Forest College

Dr Robert Bruce Nye (Associate), Philadelphia, director of the Curtis Clinic at Jefferson Medical College Hospital, has been appointed medical director of Jefferson Hospital, succeeding Dr Henry K Mohler, F A C P, who has been appointed Dean of the Medical College

Dr Rudolph H Kampmeier, F A C P, has been promoted to Associate Professor of Medicine at Vanderbilt University School of Medicine

Dr R Finley Gayle, Jr, F A C P, Richmond, has been appointed to the State Advisory Board on Mental Hygiene, State of Virginia

Dr F O Mahony, F A C P , El Dorado, has been elected first vice-president of the Union County (Ark) Tuberculosis Association

Dr William J Mallory, F A C P , has been installed as President of the Medical Society of the District of Columbia Dr Coursen B Conklin, F A C P , was re-elected Secretary-Treasurer

Dr Leon S Lippincott, F A C P , Vicksburg, Miss , has been elected Secretary-Treasurer of the Mississippi State Hospital Association

Dr L H Fuson, F A C P , St Joseph, has been elected a vice president of the Missouri State Medical Association

Dr Hillyer Rudisill, F A C P , Charleston, has been elected Secretary-Treasurer of the South Carolina X-Ray Society

Dr Edward Clay Mitchell, F A C P , Memphis, Tenn , has been elected Chairman of the Section on Pediatrics of the American Medical Association

Dr Bedford Shelmire (Associate), Dallas, Tex , was elected Chairman of the Section on Dermatology of the American Medical Association

Dr W S Rude, F A C P , Ridgetop, Tenn , has been elected vice president for middle Tennessee of the Tennessee State Medical Association

Dr J W Preston, F A C P , Roanoke, and Dr F H Smith, F A C P , Abingdon, have been reappointed by the Governor as members of the Medical Examining Board of Virginia for additional terms of four years

Dr Robert L Levy, F A C P , Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, and Dr William G Leaman, F A C P , Associate in Medicine and in charge of the Department of Cardiology, Woman's Medical College of Pennsylvania, will address the Medical Society of the State of Pennsylvania at Scranton in October on "The Therapeutic Aspects of Cardiac Pain" and "The Follow-Up Treatment of the Ambulatory Cardiac," respectively Dr Roland N Klemmer, F A C P , Lancaster, will discuss the pathology of the circulatory system

Dr Joseph H Barach, F A C P (Pittsburgh, Pa), addressed the Franklin County Medical Society (Chambersburg, Pa) on July 19, 1938 In the afternoon his topic was "Underlying Principles and Treatment of Diabetes" In the evening, he delivered an illustrated lecture on his experiences during "A Medical Tour of South America"

AMERICAN COLLEGE OF PHYSICIANS
Geographical Distribution of Members
 July 13, 1938

United States	Masters	Fellows	Associates	Total
Alabama		17	10	27
Arizona		26	4	30
Arkansas		18	6	24
California		203	42	245
Colorado		46	20	66
Connecticut		63	24	87
Delaware		7	2	9
District of Columbia		114	42	156
Florida		32	12	44
Georgia		48	33	81
Idaho			4	4
Illinois		123	51	174
Indiana		38	14	52
Iowa		35	9	44
Kansas		18	13	31
Kentucky		37	17	54
Louisiana		47	12	59
Maine		18	4	22
Maryland		69	19	88
Massachusetts		106	35	141
Michigan		139	50	189
Minnesota		100	24	124
Mississippi		14	5	19
Missouri		70	18	88
Montana		11	4	15
Nebraska		35	16	51
Nevada		2	1	3
New Hampshire		5	3	8
New Jersey		79	22	101
New Mexico		10	2	12
New York		389	178	567
North Carolina		55	15	70
North Dakota		6	1	7
Ohio		120	57	177
Oklahoma		33	19	52
Oregon		18	10	28
Pennsylvania	1	246	97	344
Rhode Island		15	12	27
South Carolina		12	9	21
South Dakota		3	4	7
Tennessee		37	15	52
Texas		89	39	128
Utah		4	5	9
Vermont		3	1	4
Virginia		50	17	67
Washington		25	15	40
West Virginia		33	20	53
Wisconsin		47	9	56
Wyoming		2	1	3
U S Possessions				
Canal Zone		10	2	12
Hawaii		11	7	18
Philippine Islands		3	1	4
Puerto Rico		6	11	17
Total (U S & Possessions)	1	2747	1063	3811

AMERICAN COLLEGE OF PHYSICIANS—*Continued*

United States	Masters	Fellows	Associates	Total
Canada				
Alberta		1	1	2
British Columbia		1	1	2
Manitoba		3		3
New Brunswick		4	1	5
Nova Scotia		1		1
Ontario		31	6	37
Quebec	1	17		18
Saskatchewan		1	1	2
Central America		2	2	4
China		5	1	6
England		3		3
Mexico		4		4
Panama		3	1	4
Siam		1		1
Turkey			1	1
Address Unknown		1		1
GRAND TOTAL	2	2825	1078	3905

OBITUARIES

DR ARTHUR THURSTON NEWCOMB

Dr Arthur Thurston Newcomb (Fellow and Life Member), aged 67 years, died at his home in Pasadena on July 19. Though Dr Newcomb had not been in good health for eight or nine years he had been getting about and doing some practice until the last few days before a recurrent heart attack caused his death.

Dr Newcomb began his practice in Pasadena forty years ago. He tried to bring back new ideas and methods of procedure from his frequent visits to other medical centers and foreign clinics. During the World War he was chief of the medical service at the Base Hospital in San Diego. He held membership in his County, State and the American Medical Associations, the Los Angeles Clinical and Pathological Society, the American Therapeutic Society and many other scientific organizations. Dr Newcomb was a senior member and one of the founders of the Huntington Memorial Hospital in Pasadena and was long an active member of the University Club. He is survived by his widow, Mrs Marie M. Newcomb, a son, Arthur Newcomb, Jr., of Pasadena, a sister and two brothers, one of whom is Dr Ralph Newcomb of Upper Lake, California.

EGERTON CRISPIN, M D, F A C P,
Regent, Southern California

DR JOHN A McVEAN

Dr John A. McVean, 59, Lakewood (Ohio) physician, died May 26, 1938, at his residence after an extended illness. Dr McVean was born in Youngstown, Ohio, and received his M. A. degree from Duquesne University in Pittsburgh in 1899. For several years he was chief chemist at the Hazelton Furnace in Youngstown, now one of the mills of the Republic Steel Corporation. He then decided to follow a doctor's career and was awarded his M. D. degree at Western Reserve Medical School in 1917. For two years Dr McVean was medical superintendent at City Hospital. He taught pathology for several years at Western Reserve. He was a member of the Cleveland Academy of Medicine and the Lakewood Chamber of Commerce, and was made a Fellow in the American College of Physicians in 1926.

A. B. BROWER, M D, F A C P,
Governor for Ohio

DR PHILIP B. MATZ

Dr Philip B. Matz (Fellow, 1927), Chief of the Medical Research Subdivision of the Veterans' Administration, Washington, D. C., died suddenly June 25, 1938, at Santa Monica, California. The cause of death was coronary disease.

Dr Matz left Washington June 1 for a two-month tour of Veterans' Administration hospitals throughout the country. He had just concluded a series of round-table conferences on tuberculosis in connection with the annual meetings of the American Academy of Tuberculosis Physicians and the National Tuberculosis Association. He had also read a paper on "The Incidence of Primary Bronchiogenic Carcinoma" before the Section on Pathology and Physiology of the American Medical Association.

Born in Baltimore, Maryland, August 25, 1885, Dr Matz received his early education in the schools of that city and New York. He held the degree of Lit B from Mather College, Kansas City University, Kansas City, Kansas, and M D from Long Island College of Medicine, Brooklyn, New York (1908). In addition he did postgraduate work at Kansas University, St Louis University, Chicago University, Rockefeller Institute for Medical Research, New York City, and Michael Reese and Cook County Hospitals, Chicago, Ill.

Dr Matz entered the government service in 1909 when he was appointed Assistant Surgeon, National Military Home, Leavenworth, Kans., and assigned as Chief of Laboratory. His government service was continuous from that date except for the four-year period 1914-1917, during which time he conducted private laboratories in Kansas City and Leavenworth, Kans., and served as consultant serologist at the Federal Penitentiary, Leavenworth, Kans.

In August 1917, Dr Matz was commissioned 1st Lt M C, U S Army, and assigned to active duty as Chief of Laboratory Service, Base Hospital, Camp Travis, Texas. He was promoted to Captain in February 1918 and continued as Chief of Laboratory Service. A report of his intensive work during the influenza epidemic of 1918 may be found in an article entitled "Laboratory Studies in Influenza at Camp Travis, Texas," published in the *American Journal of the Medical Sciences*, November 1919.

After the war Dr Matz was commissioned as Surgeon (Reserve), U S Public Health Service, and served as Chief of the Laboratory Service at U S Public Health Service Hospitals, Dansville, N Y, Ft McHenry, Md, Maywood, Ill, Camp Logan, Texas, and Legion, Texas. His successful record as pathologist in the field organization of the Veterans' Administration and his active interest in research work led to his appointment in August 1925 to the position of Chief of Medical Research in Central Office, which he held continuously until the time of his death. In supervising medical research in the 81 hospitals and 22 dispensaries operated by the Veterans' Administration, Dr Matz was particularly interested in the various diseases found in the ex-service men. He was the author of numerous studies in serology, cardiology and other circulatory diseases, tuberculosis, arthritis, cancer, diabetes mellitus, silicosis, etc. In 1926 he was appointed a member of a special Board convened by the Government to study the residuals of warfare gassing.

He belonged to many medical societies including the American Medical Association, the American College of Physicians, the American Society of Clinical Pathologists, the American Academy of Tuberculosis Physicians, the Kansas State Medical Society, and the Clinical Club of Washington. He was also a member of the American Legion and the Military Order of the World War, the Torch Club of Washington, and the Sojourners Lodge No 51.

Dr Matz was a man of great charm, a soldier with a most enviable record, a physician of exceeding skill, and a writer of rare ability. He was imbued with an unselfish spirit of devotion to duty. His numerous friends in and out of the Veterans' Administration will miss him sadly and in his passing the medical profession at large has lost one of its most valued associates. While there are many salient points with respect to his honored career, it is difficult in a life so full of accomplishments to choose for particular commendation any one achievement.

Dr Matz is survived by his widow, Mrs Eleanor Crampton Matz, his mother, three brothers, and three sisters.

He was buried with full military honors in the National Homes Cemetery, Fort Leavenworth, Kansas, Thursday, June 30, 1938.

CHARLES M GIFFITH, M D , F A C P ,
Washington, D C

DR RALSTON LATTIMORE

Dr Ralston Lattimore, Savannah, Ga , aged 67, died on April 20, 1938, at his home after a long illness. He was a native of Savannah. Dr Lattimore attended the Savannah High School and Moreland Park Military Academy and received the degree of doctor of medicine from Columbia University College of Physicians and Surgeons in 1893. For three years after graduation he served as house physician at Mount Sinai Hospital in New York, then for a year he was active physician at the Sloan Maternity Hospital. Later he took special postgraduate work in Berlin and Vienna and then began the active practice of medicine in Savannah. Dr Lattimore had always been associated with organized medicine and held many honorary offices. He was author of the Vital Statistics Bill, which was passed by the Georgia Legislature in 1915 while he was chairman of the Committee on Public Policy and Legislation for the Medical Association of Georgia, the Medical Practice Bill was passed while he was President of the Georgia State Medical Association, 1913-14. He was a member of the Medical Association of Georgia, Southern Medical Association, American Medical Association and a Fellow of the American College of Physicians since 1921.

GLENVILLE GIDDINGS, M D , F A C P ,
Governor for Georgia

DR GEORGE EMILE NEUHAUS

George Emile Neuhaus (Fellow) was born in Berlin, Germany, in 1866 and died in Omaha, Nebraska, on May 15, 1938

He was educated at Bellevue Hospital Medical College where he received his M D degree in 1891. He had postgraduate study at the Harvard University Medical School, Boston Psychiatric Institute and the Neurological Institute of New York. He practiced first in New York, leaving there to become Medical Director of the Mount Airy Sanatorium at Denver, Colorado, from 1907 to 1922, and locating in Omaha, Nebraska, in 1922.

Dr Neuhaus, at the time of his death, was Associate Professor of neuropsychiatry at Creighton University School of Medicine, and Attending Neurologist at St Catherine's Lutheran and St Joseph's Hospitals. He was a member of the Douglas County Medical Society, Nebraska State Medical Association, American Medical Association, American Psychiatric Association, Central Neuropsychiatric Society, Midwest Clinical Society and a Fellow of American College of Physicians since 1920.

Dr Neuhaus was an earnest student with broad and unlimited interests in his chosen field. He was a kind and wise counsellor and his death is a great loss both to the medical profession and to the community.

WARREN THOMPSON, M D , F A C P ,
Governor for Nebraska

DR FREDERICK LEONARD FENNO

Dr Fenno of New Orleans, Louisiana, aged 43, died suddenly on July 20, 1938. In the passing of Dr Fenno the medical profession of the City of New Orleans and the State of Louisiana has lost one of its most brilliant and popular members and the American College of Physicians has lost one of its most useful and enthusiastic Fellows.

Dr Fenno was born at Plainfield, New Jersey, in 1895. He attended public schools in Plainfield, New Jersey, and in New Orleans, Louisiana. He received his M D degree from Tulane University of Louisiana School of Medicine in 1917. He has served as instructor in Clinical Neurology in Tulane University of Louisiana School of Medicine. He was a member of the Orleans Parrish Medical Society, Louisiana State Medical Society, Southern Medical Association, American Medical Association, American Public Health Association and the American Association of School Physicians. He had been a Fellow of the American College of Physicians since 1928. In his earlier experience he served as assisting consulting neurologist at the Eye, Ear, Nose and Throat Hospital and the Illinois Central Railroad Hospital of New Orleans, and he was senior visiting neurologist of the Charity Hospital and was medical director of the Orleans Parrish Public Schools.

For years Dr Fenno had devoted himself to the practice and teaching of neurology, his chosen specialty, and many of the younger practitioners of the South have heard with sorrow and regret of the untimely death of their former teacher

He was very popular with the members of the Orleans Parrish Medical Society, who, recognizing his ability as an organizer and executive, selected him as Chairman of the Entertainment Committee for the next annual meeting of the College which is to be held in New Orleans

Dr Fenno was a pleasing and affable type of personality and was loved and admired by his many friends

He was public spirited and active in civic and social affairs and his untimely passing leaves a void in the hearts not only of the medical profession, but of the public whom he served

JOSEPH E KNIGHTON, M D , F A C P ,
Governor for Louisiana

a culture of *B. coli* before treatment we found that the *B. coli* had disappeared but found other organisms *B. proteus*, diphtheroids, Friedlander's bacillus and *Streptococcus viridans*

pH of the Urine The pH of the urine in these patients varied from 5.0 to 7.5. The pH of most of most of them (18 cases) was found to be from 5.0 to 6.5.

Reactions No reaction occurred in 11 cases. Twelve patients complained of some of the following symptoms during the first few days of medication: dizziness, weakness in the legs, tingling sensation in the fingers and toes. One of these developed a temperature of 101° for 24 hours, which subsided when medication was stopped and did not recur when it was started again. One patient developed a very acute attack of gastroenteritis with nausea, vomiting, diarrhea and fever. All these symptoms disappeared within 48 hours after medication was discontinued. In one case the dizziness and headache were so marked after the first few doses that medication had to be stopped immediately and we have been unable to give this patient any of the drug, even a 5 grain dose, without a reaction. Therefore no further treatment was attempted with this drug in this case.

Present Condition Nine cases (36 per cent) are entirely well. Eight cases (32 per cent) showed marked improvement. Two showed marked improvement for several weeks and then had recurrence of all previous symptoms. Two showed slight improvement. Four showed no improvement. Therefore 68 per cent of this group are either entirely well or show marked improvement.

Dosage Eighty grains of sulfanilamide were given each patient the first day and 40 grains per day for the next six days. After the first week the dosage varied from 20 to 30 grains per day. If reaction occurred, the drug was immediately discontinued for one to two days. On continuing the drug the dosage was started at 15 grains per day and gradually increased until 30 or 40 grains per day were taken. In several instances the drug could not be tolerated if more than 10 to 15 grains per day were taken.

SUMMARY

A careful study of the value of sulfanilamide in the treatment of 25 patients with infections of the bladder or upper urinary tract or both, showed the following:

1. Most of the patients had infections of long duration (1 to 5 years) which had not responded to the various, usual methods of treatment.
2. Many varieties of organisms were found on culture of kidney and bladder urine before treatment was started.
3. Most of the patients (16 cases) showed symptomatic improvement, or clearing of the urine within one week.
4. Before treatment the urine was cloudy in every case but two (in which it was hazy), and after treatment the urine became clear in 15 cases and hazy in 6 cases. Only four cases showed no improvement.

5 The best results were obtained in those cases where we found the *B coli* and the streptococcus. We obtained no improvement in those cases where the *B proteus*, Friedlander's bacillus or *B pyocyaneus* were found.

6 No serious reactions occurred.

7 Since, in the final analysis, 17 of these patients (68 per cent) are now entirely well or show marked improvement, we believe that sulfanilamide is a very valuable drug in the treatment of infections of the bladder and upper urinary tract.

However, in view of the widespread and promiscuous use of this drug in infections of the genito-urinary tract, we wish to state most emphatically, that no patient should be given this drug before a complete urologic study has been carried out. This study may reveal a pathological condition which may require surgery or some other form of treatment and sulfanilamide in such instances may be valueless and prove harmful.

The indiscriminate use of this drug, without careful and complete preliminary studies, must be condemned.

REFERENCES

- 1 DOMAGK, G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, *Deutsch med Wchnschr*, 1935, **lx**, 250.
- 2 SCHERBER, G. Zur lokalen und allgemeinen Behandlung des Rotlauf, in letzterer Beziehung mit besonderer Darstellung der Anwendung des Farbstoffpräparates Prontosil (Streptozon Präparat 5214) wie der Behandlungsergebnisse mit Omnadin, *Wien med Wchnschr*, 1935, **lxxxv**, 284, 346, 376, Die Behandlung des Rotlauf mit interner Prontosiltherapie kombiniert mit intravenösen Omnadinjektionen, *ibid*, 1935, **lxxxv**, 783, Zur Behandlung der verschiedenen Formen des Pemphigus chronicus mit Antileprol und Prontosil, *ibid*, 1936, **lxxxvi**, 22.
- 3 ANSELM, E. Unsere Erfahrungen mit Prontosil bei Puerperalfieber, *Deutsch med Wchnschr*, 1935, **lxi**, 264.
- 4 KRAMER, W. Ueber Erfahrungen bei der Erysipelbehandlung mit Prontosil, *München med Wchnschr*, 1936, **lxxxiii**, 608.
- 5 COLEBROOK, L., and KENNY. Treatment of human puerperal infections and of experimental infections in mice, with prontosil, *Lancet*, 1936, **i**, 1279, Treatment with prontosil of puerperal infections due to hemolytic streptococci, *ibid*, 1936, **ii**, 1319.
- 6 LONG, P. H., and BLISS, E. A. Para-amino-benzene-sulfonamide and its derivatives, *Jr Am Med Assoc*, 1937, **cviii**, 32.
- 7 BUTTLE, G. A. H., GRAY, W. H., and STEVENSON, D. Protection of mice against streptococcus and other infections by para-amino-benzene-sulfonamide and related substances, *Lancet*, 1936, **i**, 1286.
- 8 PROOM, H. Therapeutic action of para-amino-benzene-sulfonamide in meningococcal infection of mice, *Lancet*, 1937, **i**, 16.
- 9 COOPER, F. B., GROSS, P., and MELLON, R. R. Action of para-amino-benzene-sulfonamide on Type III pneumococcus infections in mice, *Proc Soc Exper Biol and Med*, 1937, **xxxvi**, 148.
- 10 ROSENTHAL, S. M. Chemotherapy of experimental pneumococcus infections, *Public Health Rep*, 1937, **lii**, 48.
- 11 DEES, J. E., and COLSTON, J. A. C. The use of sulfanilamide in gonococcal infections, *Jr Am Med Assoc*, 1937, **cviii**, 1855-1858.
- 12 Report of Council on Pharmacy and Chemistry, *Am Med Assoc Sulfanilamide and related compounds*, *Jr Am Med Assoc*, 1937, **cviii**, 1888-1890.

A BROADER VIEW OF POSTMORTEM EXAMINATIONS

By ALAN GREGG, *New York, N Y*

Mr President and Gentlemen

I shall not explore the limits of your patience or abuse the courtesy of your attention by proffering in twenty minutes' time the brief of a long debate or the essence of a book. Let me rather submit to you only three scattered experiences of the past few years and conclude with a question which you are better qualified to answer than any other persons I know. The experiences may seem unrelated at first but I trust a certain coherence will be evident in due course, and I hope eagerly for as many answers later from you individually as may be possible since a sound understanding of any question calls for many corrections and qualifications.

I belong to a dinner club that plans a series of meetings at which a representative of each of several professions will advise the rest of us how the services of his profession can best be used by the laity. An architect, for example, will tell the rest of us how we can best make use of an architect's knowledge and experience, how to protect ourselves against incompetence or selfishness, what the layman should know of the architect's professional ethics and usages, on what terms does the architect give his best services, where lie pitfalls of misunderstanding between him and his client, what course, in short, would be wisest for the client to pursue in order to put the architect in the easiest position to give his services most effectively. And similarly we shall call upon some of the other professions, for example, an investment counselor, a newspaperman, an insurance expert, a lawyer, and—a physician. For in a society so differentiated into special callings as is the society of our times we are all laymen in everything but our own professions. And I would hold it to be wise to learn whatever possible of how to approach and maintain effective relations with other professions than one's own, and to learn this at a time divorced if not remote from the pressure of immediate need. It is probably equally wise too for every profession to cultivate public understanding rather than merely to court general approval.

And so from this dinner club plan inevitably I had and indeed still have the general question before me: "What advice could be given to laymen on how best to utilize a doctor's services?" I have postponed an answer which deserves so much reflection. A number of other questions have emerged in the meantime. To restate the matter let us repeat the formula for the architect, but this time in terms of the physician. How can the layman best make use of the physician's knowledge and experience? How can he

* Read before the American College of Physicians, New York, N Y, April 4, 1938

protect himself against incompetence and selfishness? What should the layman know of the physician's professional ethics and usages? On what terms does the physician give his best services? Where lie pitfalls of misunderstanding between physician and patient? In short, what course would be wisest for the layman to pursue in order to get the most benefit from a physician? Mark you, how to choose a good doctor is not within this question, that is another story. It is how to get the best from him once the choice is made. Are there any steps the layman can take to ensure as well as encourage the best of medical performance—and has he ever been told them by someone unrelated to the occasion of their use?

The next experience has been spread over the past seven years—I have realized the extraordinary fluidity of the population of the United States in contrast to the stability of residence of the Europeans. Travel by automobile has not only replaced much travel by train but it has extended the number and range of trips, excursions, visits, and it has encouraged moving and changes of residence. We think nothing of distance. We are the most restless and movable people on earth—or above it. Consequently a seriously large number of persons, separately or in families, must call an unknown physician in some unfamiliar place of residence. Now this is done usually on a basis that scarcely deserves the words *choice* or *selection*. The situation lacks the reassurance of long acquaintance with our informants or advisors. It may be hurried and urgent. It may be incredibly haphazard. Doctors are often chosen under circumstances which make it more than ever important that mutual understanding attend their relationship to patients. And so it was my second experience to realize that in America especially, because of its constantly moving population, the layman needs a map of our ways. He needs to be told how we can best help him.

Lastly an experience of three years ago in the clinicopathological conference room of a well known medical school. I saw by chance a blackboard lying on its side in apparent neglect. On it were written the percentages for the preceding quarter of postmortem examinations secured on deaths (*a*) on the private wards and (*b*) on the public wards, 13 per cent of the private patients who died came to post mortem, 82 per cent of the patients on the public wards came to post mortem. Quite appropriately that table of figures on post mortems was lying on its side, for it bore evidence of neglect of one of the most enlightening and stimulating practices we physicians know—the postmortem examination. We know the post mortem can and does improve our efforts at diagnosis, we know it is the terror of the casual guesser, we know it is a reward to an eager and honest doctor even when it is a stark corrective, we know it increases our competence and knowledge—in sum, we know the post mortem serves as a merciless incentive to the best we have in us as physicians.

But does the layman know? Let me draw these three experiences together now in the question I wish to ask you. Shall the layman be told

this incentive to our best performance? Is it not true that if a layman wishes to get the best possible service from a physician he would be wise to say at the outset of an illness—"Now Doctor, there's one thing I should like to have clear if worse comes to worst there is to be a post mortem"?

In increasing measure the American of all classes uses a hospital. *We* know that he would be wise to demand rather than reluctantly concede the performance of a postmortem examination. But does he know it? I doubt it. And is it wise for him and for us that he should remain any longer uninformed of a safeguard within his reach?

I have never heard the layman's interest mentioned in discussions of post mortems. The postmortem examination has been emphasized as a way to advance scientific knowledge, or it has been thought of as a generous concession to the forgivable curiosity of a beloved doctor, or it has been urged as a method without equal in maintaining staff efficiency in hospitals—but I would inquire whether anyone unprejudiced and remote from the event has ever shown the laity where its interests lie in the matter of post mortems? Is it reasonable to tell the layman that the warning of a post mortem might urge and convert an incompetent doctor in time from proud isolation to prudent consultation? Is it reasonable to say that the mention of a post mortem would never lessen the interest of a competent and trustworthy doctor? Is it reasonable to state quite candidly that in the request for post mortems the public has a means of protecting its own interests? To have an understanding with a physician that if death comes an autopsy will follow involves, as it seems to me, no extra risk whatever to the patient.

The question perhaps suggests that two assumptions are being taken for granted—one that there are no great objections in the lay mind to post mortems, and the other that there are enough competent pathologists ready for such a revolutionary change. Neither of these assumptions is true at present, but both are capable of becoming true gradually and at a rate that will not jeopardize the change. Both were even more valid objections when hospitals began to secure post mortems. If, as the phrase goes, "no effort is to be spared to improve the patient's chances" is it not time to have it widely known that experience shows that the practice of post mortems has improved the patient's chances?

There is real need for each profession to teach the laity how best to use its services. In America where with increasing frequency doctors' services are called in ignorance of their capacities, the ways of protecting the laity are of importance. Among other means too numerous to mention at this time one simple suggestion is then here offered for your comment: the performance of postmortem examinations, in that it has greatly improved our efforts as doctors, should be known by the laity as an advantage also within their power to demand.

So the essential point is this: do you endorse my view that one simple but powerful piece of advice in his own protection the layman could wisely

be given is this—"Explain to whomever you call that if death comes a post mortem will be required"? It may be grim advice—but in the cause of good medicine we do not shirk giving grim advice. It may not be heeded—we have had that experience too. But it can be understood—and because it is in the interest of the patient, the post mortem can change gradually from being hated and feared and avoided to being used and trusted and steadily perfected. We have known similar transitions in the past. Already, as many of you know, the clinicopathological conference is the wonder and admiration of many of our foreign visitors, who see in it a candor and fearlessness altogether to the credit of American medicine.

CASE REPORTS

BENZEDRINE AND PAREDRIINE IN THE TREATMENT OF ORTHOSTATIC HYPOTENSION, WITH SUPPLEMENTARY CASE REPORT

By HORACE MARSHALL KORN, M D, and WILLIAM LLOYD RANDALL, M D,
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In January, 1937, in a report¹ of our experience with benzedrine in the treatment of orthostatic hypotension, we pointed out that if amounts of either benzedrine or ephedrine sufficiently large to maintain the blood pressure within normal limits were employed for more than a few days at a time, it became difficult, even with full doses of the various barbiturates, to overcome the consequent insomnia. When this statement caught the eye of Mr W F Thompson, of the Smith, Kline and French Laboratories, he suggested that we try paredrine (beta-parahydroxyphenylisopropylamine), a related amine, which, according to preliminary pharmacologic studies,^{2,3,4} has a greater pressor action than benzedrine and none of its stimulating effect on the central nervous system, and kindly offered to supply enough paredrine for the experiment.

The results which we obtained are summarized in the following table, the measurements are representative of a large series.

TABLE I

	Column 1	Column 2	Column 3	Column 4		Column 5	
	Untreated	Paredrine, 20 mg every half hour from 8 30 a m to 6 p m Total 400 mg	Benzedrine, 10 mg every hour from 8 a m to 4 p m Total 90 mg	Benzedrine, 20 mg at 6 and 7 a m Total 40 mg Paredrine, 40 mg every 2 hours from 8 30 a m to 2 30 p m Total 160 mg		Benzedrine, 20 mg at 6 and 7 a m Total 40 mg	
	3 p m	2 30 p m	2 30 p m	8 30 a m	2 30 p m	9 a m	3 p m
Supine	120/80	125/85	140/95	122/85	150/95	108/76	120/85
Sitting	80/60	115/90	135/90	108/80	138/90	84/55	112/85
Standing	60/?	95/70	98/75	65/50	100/80	50/?	65/55

A comparison of the data tabulated in columns 2 and 3 shows that the pressor effect of paredrine was practically equal to that of benzedrine, but the patient preferred benzedrine because it invigorated and stimulated him, whereas pare-

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From the Department of Internal Medicine, State University of Iowa

dine had no appreciable effect on his lassitude. This suggests that the chronic fatigue which is so characteristic of orthostatic hypotension is not due entirely to the low arterial pressure. No insomnia was produced by parendrine, even with doses as large as 400 mg. a day, contrariwise, it seemed to exert a soporific effect, for the patient not only slept soundly at night, but frequently dozed during the day. The next step was to use benzedrine early in the morning and parendrine throughout the rest of the day, which proved to be the ideal arrangement. After much experimenting with the method of administration, the schedule at the top of column 4 (table 1) was ultimately chosen as the optimum. A comparison of columns 4 and 5 shows the sustaining effect of the parendrine. No unpleasant incidental effects of either drug were noted.

SUPPLEMENTARY CASE REPORT

Throughout the year that had elapsed since our first report,¹ the patient's average daily dose of benzedrine was 80 to 100 mg. Occasionally he increased it to 150 mg. This enabled him to live a quiet life in comfort, but not to do much work. He had been perspiring quite freely, and had noticed that he was no longer entirely impotent or devoid of libido. His basal metabolic rate, originally minus 10 per cent, was now minus 25 per cent. Desiccated thyroid, in doses of 4 grains a day, increased it within 10 days to minus 9 per cent without affecting the blood pressure appreciably.

A previously unrecognized factor in the patient's disability—paroxysmal hypoglycemia—was discovered while he was in the hospital for the parendrine experiment. Our suspicions were aroused when he complained that occasionally he was overtaken rather suddenly by extreme weakness, tremor, nervousness, and hunger which did not seem to him to be due to his orthostatic hypotension because he had noticed that these particular symptoms were unrelated to posture and could always be relieved by the ingestion of food. There was no opportunity to observe the patient during one of these attacks, but 90 minutes after the administration of 50 grams of glucose his blood sugar had fallen to 26 mg. per cent and he was having hypoglycemic symptoms which he recognized at once. Reinvestigation of the history then disclosed the fact that he had had similar seizures many years before. Either they had ceased temporarily or had been overwhelmed by the manifestations of his orthostatic hypotension. That benzedrine might have educed them seemed unlikely. They disappeared entirely when his daily intake of protein was increased from about 75 grams to 120 grams.

We were unable to discover the cause of the patient's increasing anemia. The hemoglobin content of his blood had fallen from 72 to 62 per cent, and the erythrocyte count from 3,790,000 to 2,750,000. There was no history of hemorrhage, the bleeding time and coagulation time were normal, the platelet content of the blood was normal, and the erythrocytes were normally resistant to hemolysis by hypotonic salt solution. The feces were examined for blood many times, but only negligible quantities were found, and roentgenologic examination of the alimentary tract disclosed no evidence of disease. There was no retention of nitrogen in the blood.

COMMENT

This patient's orthostatic hypotension, paroxysmal hypoglycemia, and low basal metabolic rate suggest the possibility of an endocrine disturbance involving the adrenal, thyroid and pituitary glands and the isles of Langerhans

Paredrine is a very useful adjuvant to benzedrine in the symptomatic treatment of orthostatic hypotension

REFERENCES

- 1 KORN, H M, and RANDALL, W L Orthostatic hypotension treated with benzedrine, *Am Heart Jr*, 1937, xiii, 114
- 2 ALLES, G A The comparative physiological actions of the di-beta-phenylisopropylamines I Pressor effect and toxicity, *Jr Pharm and Exper Therap*, 1933, xlvii, 339
- 3 NATHANSON, M H Action of parahydroxyphenylisopropylamine on induced cardiac standstill, *Proc Soc Exper Biol and Med*, 1937, xxxv, 627
- 4 ABBOTT, W O, and HENRY, C M Paredrine (beta-4-hydroxyphenylisopropylamine) A clinical investigation of a sympathomimetic drug, *Am Jr Med Sci*, 1937, cxciii, 661

TOLERANCE TO BENZEDRINE SULFATE

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IN 1935 Prinzmetal and Bloomberg¹ introduced benzedrine (phenylisopropylamine), a comparatively new sympathomimetic for the treatment of narcolepsy Its dramatic success in this condition stimulated many investigations of additional therapeutic indications for the use of the systemic effects of benzedrine, as well as verification of its value in narcolepsy² It has been demonstrated that benzedrine relaxes gastrointestinal spasm³, ameliorates apathy and depression in normals and in neurotic persons,⁴ and in post-encephalitic Parkinsonism⁵, aborts marked drop in blood pressure during spinal anesthesia⁶, and prevents syncope caused by orthostatic hypotension⁷ We have found it efficacious in the prevention of carotid sinus syncope of the vagal and depressor type⁸ No reports of addiction, and only one report of tolerance to benzedrine have been reported to date⁹ In the course of a study on the efficacy of benzedrine sulfate in the control of carotid sinus syncope an appreciable degree of tolerance to benzedrine was elicited The following case forcibly brought this fact to our attention

CASE REPORT

A B, a male patient, 24 years of age, is one of a series of patients with hyperirritable carotid sinus reflex we have been studying For the past six years this patient has had syncopal attacks occurring about six times monthly During these attacks there are loss of consciousness and generalized convulsions The attacks cease within half a minute, and are not followed by confusion Seizures can be induced by pressure with the fingers over the right carotid sinus Pressure maintained in this way for 10 seconds causes slowing of the pulse from 70 to 22, decrease in blood pressure from 110 systolic and 70 diastolic to 80 systolic and 60 diastolic and generalized convulsion lasting but six seconds after pressure is released Atropine gr 1/60 intravenously was ineffective in preventing induced attacks whereas

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epinephrine 0.5 c.c. subcutaneously was efficacious in this regard. This case falls into the type of sinus syncope which Weiss¹⁰ and his colleagues have well classified as embodying both the vagal response (with sino-auricular or auriculo-ventricular block) and the depressor response (with vasodilatation and hypotension). Epinephrine or ephedrine prevents the vagal response by direct ventricular stimulation as a result of which the ventricles assume an independent rhythm sufficiently rapid to prevent the syncope which would otherwise follow vagal heart block. In the depressor type of hyperirritable carotid sinus, these sympathomimetic drugs abort attacks by constricting the small blood vessels, thus abolishing vasodilatation and resulting syncope.¹⁰

The patient was therefore placed upon ephedrine sulfate therapy which Weiss et al.¹⁰ have demonstrated to be efficacious for the depressor and vagal types of sinus syncope. Although efficacious, the action of ephedrine proved short lived. Generally from $\frac{3}{8}$ to $\frac{1}{2}$ grain of ephedrine has been recommended for the depressor type of sinus syncope. But even in one grain doses ephedrine aborted induced attacks for not more than half to one hour in this patient. We therefore resorted to benzedrine, which is a sympathomimetic drug closely related to epinephrine and ephedrine. The patient was given 20 mg. of benzedrine sulfate orally. At intervals attempts were made to induce sinus attacks. It was found that benzedrine prevented cardiac slowing, hypotension and syncope, even when sinus pressure was made, over a period extending from 25 minutes after the oral administration to 4 hours after medication.

Thereafter 20 mg. of benzedrine three times daily prevented induced and spontaneous seizures satisfactorily for 10 days. On the tenth day a spontaneous seizure occurred. We at first were at a loss to account for this as medication had not been interrupted. On attempting pressure over the right carotid sinus, syncope could be induced repeatedly. As a result, 30 mg. of benzedrine sulfate were given thrice daily with again a cessation of spontaneous and induced seizures. This phenomenon recurred several times and the dosage was raised 10 mg. each time. At intervals varying from 7 to 10 days tolerance for the larger doses necessitated repeated increments of benzedrine. At one time the patient was receiving as much as 250 mg. of benzedrine sulfate daily (50 mg. every three hours). Not only was it necessary to increase the individual doses but it became necessary to give the medication at shorter intervals, namely every three hours, as the effects did not persist over the longer period as previously. At this point therapy was withdrawn for several days. Then the initial small doses of benzedrine sulfate which had been effective originally were again administered. Tolerance had disappeared in the interval and the benzedrine was once more as effective as on first administration.

This procedure succeeded in preventing spontaneous and induced seizures for another week to ten day interval. After this time tolerance reappeared, and it was necessary either to raise the dosage or omit the benzedrine for two to three days, and then renew the small doses.

Although insomnia was present for the first night, benzedrine thereafter did not interfere with sleep even when given in large doses.

COMMENT

The greater number of observers who have reported on the systemic use of benzedrine have failed to note the development of tolerance. Solomon, Mitchell and Prinzmetal⁵ "have seen no evidence to indicate either an increasing tolerance to the drug or habit formation." As much as 160 mg. a day for three weeks was taken by one of their patients without apparent harmful effect. They make the interesting statement that the first patient with narcolepsy reported by Prinzmetal and Bloomberg¹ is still taking the same dose after three years.

Nevertheless, as in this case, those who have given benzedrine invariably comment on the fact that it often causes insomnia at the outset^{1, 4, 5}. This disappears in a few days (generally one to three days) despite continuance of the initial dosage. Solomon and his colleagues⁵ stated that 11 of their postencephalitic patients did not sleep well the first few nights following the beginning of benzedrine treatment but that the relative insomnia usually lasted no more than three days and usually wore off without the necessity of reducing the dosage.

Furthermore they noted that dizziness or undue nervous tension which appeared for a day or two at the beginning of treatment in six cases, recurred in three cases when the dosage was increased later, but was only temporary. Excessive restlessness and excitement occurring temporarily in two cases were eliminated by halving the dose, and even when the dosage was raised later these symptoms did not reappear. We interpret these facts as evidence of tolerance to benzedrine's undesirable effects, although we are fully cognizant that these observers noted no tolerance to the desired therapeutic effect of benzedrine such as is reported here.

Davis and Shumway-Davis treating a case of orthostatic hypotension with benzedrine found it necessary, after a time, to increase the previously effective benzedrine doses, and their other case so treated in whom "all symptoms had disappeared," later increased his benzedrine dosage himself because the additional doses made him feel "more comfortable."⁷

Wilbur et al.⁹ reported that, while benzedrine abolished the apathy in many patients suffering from a state of chronic exhaustion, in an appreciable number of these patients the beneficial effects of the benzedrine wore off at the end of 3 to 16 weeks of continued administration of the drug. In their group of 21 psychoneurotic depressed patients benefited by benzedrine, "six reported that in spite of continued medication the initial favorable results were not repeated after the first week. Because benzedrine failed to relieve their condition, an additional six patients discontinued its use in one month and three more patients discontinued its use at the end of three months."

Much like our experience with the reported case, Wilbur et al.⁹ also found that occasionally, intermittent use of benzedrine proved more satisfactory than continuous administration.

SUMMARY

An instance of tolerance to benzedrine sulfate is reported. Benzedrine sulfate was initially effective in preventing the depressor type of response and syncope due to a hyperirritable carotid sinus in a male of 24.

Tolerance to benzedrine, exemplified by recurrence of sinus hyperirritability, developed on the tenth day.

Thereafter at 7 to 10 day intervals it was necessary either to increase the dosage or omit the drug for several days in order to maintain the therapeutic efficacy of benzedrine.

REFERENCES

- 1 PRINZMETAL, M, and BLOOMBERG, W. The use of benzedrine for the treatment of narcolepsy, *Jr Am Med Assoc*, 1935, cv, 2051-2054.
- 2 ULRICH, H, TRAPP, C E, and VIDGOFF, B. The treatment of narcolepsy with benzedrine sulfate, *ANN INT MED*, 1936, ix, 1213-1221.

- 3 MYERSON, A, and RITVO, M Benzedrine sulfate and its value in spasm of the gastrointestinal tract, Jr Am Med Assoc, 1936, cvii, 24-26
- 4 MYERSON, A Effect of benzedrine sulfate on mood and fatigue in normal and in neurotic persons, Arch Neurol and Psychiat, 1936, xxxvi, 816-822
- 5 SOLOMON, P, MITCHELL, R S, and PRINZMETAL, M The use of benzedrine sulfate in postencephalitic Parkinson's disease, Jr Am Med Assoc, 1937, cviii, 1765-1770
- 6 TOVELL, R M Control of blood pressure during spinal anesthesia preliminary report, Proc Staff Meet Mayo Clinic, 1936, ii, 585-588
- 7 DAVIS, P L, and SHUMWAY-DAVIS, M Orthostatic hypotension the treatment of two cases with benzedrine sulfate, Jr Am Med Assoc, 1937, cviii, 1247-1249
- 8 ROBINSON, L J Benzedrine sulfate in the treatment of syncope due to a hyperactive carotid sinus reflex, New Eng Jr Med, 217 (to be published)
- 9 WILBUR, D L, MACLEAN, A R, and AILEN, E V Clinical observations on the effect of benzedrine sulfate, Jr Am Med Assoc, 1937, cx, 549-554
- 10 WEISS, S, CAPPS, R B, FARRIS, E B, JR, and MUNRO, D Syncope and convulsions due to a hyperactive carotid sinus reflex, Arch Int Med, 1936, lvi, 407-417

PRIMARY SARCOMA OF THE PERICARDIUM, REPORT OF A CASE *

By P G BOMAN, M D, F A C P, *Duluth, Minnesota*

PRIMARY tumors of the heart and pericardium are rare, and a definite diagnosis of such a condition is seldom made except at autopsy In reviewing this subject, Yater ¹ states that more than 150 cases of primary tumor of the heart have been reported in the literature, and Lymburner ² in 1934 found 256 such cases recorded While there is some difference of opinion as to the number of authenticated cases reported, it is evident that these cases are not common and that they are of considerable medical interest

The great majority of the reported primary tumors are benign Less than 20 per cent are malignant Of the malignant group almost all the cases reported are of primary sarcoma of the heart and pericardium In view of this it is interesting to note that Peilstein ³ in 1918 found only 30 cases of primary sarcoma recorded, and added 1 additional case of his own Yater ¹ in 1931 stated that 15 additional cases had been reported in the interim Since that time, in this country, Morris ⁴ in 1933, and Barnes, Beaver and Snell ⁵ in 1934, reported two additional cases Of these reported cases, 15 were spindle cell sarcomata, 14 round cell sarcomata, 4 giant cell sarcomata, 3 myxosarcomata, 3 fibrosarcomata, 4 mixed cell sarcomata, 1 angiosarcoma, 1 lymphosarcoma, 1 liposarcoma and 1 rhabdomyosarcoma

From the reports in the literature it is apparent that the majority of sarcomata of the heart arise from the auricles and that relatively few originate in the pericardium, only 10 having been reported as primary in the pericardium according to Yater's ¹ review

The symptomatology of tumors of the heart varies greatly In some instances symptoms of cardiac origin are not present up to the time of death, while in others symptoms of cardiac involvement and cardiac failure appear at varying times before death Sudden deaths, both with and without previous

* Presented at the meeting of the Minnesota Heart Society, December 7, 1935
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cardiac symptoms, are reported, and symptoms suggestive of subacute bacterial endocarditis have been recorded. Arrhythmias and conduction disturbances likewise may be present. Naturally, the symptoms will vary according to the location of the tumor and the portion of the heart which is primarily involved. In order to classify the symptomatology, Yater¹ has used the following division of symptoms

(A) Clinical types not suggestive of tumor of the heart

- 1 Absence of symptoms referable to the heart
- 2 Symptoms of cardiac embarrassment terminally
- 3 Symptoms of congestive heart failure
- 4 Sudden death
- 5 Symptoms suggestive of subacute bacterial endocarditis

(B) Clinical types suggestive of tumor of the heart

- 1 Heart block
- 2 Symptoms referable to location of tumor other than heart block
- 3 Symptoms of cardiac dysfunction developing without apparent cause in a patient with a known malignant process
- 4 Accumulation of hemorrhagic fluid, pericardial and pleural
- 5 Suggestive roentgen observations

This division is of particular value in the study of the reported cases. Actually few symptoms are found which are constant and of diagnostic help.

In primary malignant growth of the pericardium one may find many of the symptoms usually associated with pericarditis, and the course of the former may so closely simulate that of the latter as to lead to a diagnosis of pericarditis, as occurred in the case herewith reported. There does not appear in the literature any case of primary malignant neoplasm of the pericardium which has been diagnosed ante mortem.

CASE REPORT

History A white male, aged 27, was first seen on April 1, 1931, at which time he complained of precordial pain and palpitation of the heart of one month's duration. Immediately preceding the onset of these symptoms he had an attack of "influenza" lasting one week. During convalescence he cranked a car, after which he felt very weak and short of breath, his heart beat rapidly and he noticed a generalized soreness and stiffness of the chest and of the right shoulder. After one week the soreness and stiffness disappeared, but attacks of pain in the precordium, with radiation to the right shoulder, continued and increased in frequency and severity. The pain was of a pressure type, and the patient stated that it felt like "a ton of bricks was laid on my chest." He noted that the pain was increased on swallowing and after exercise. Night sweats were present, his appetite became poor, and there were indications of weight loss.

Past History Except for measles in childhood and tonsillectomy there was no history of any previous illnesses.

Family History Father living and well. Mother living but has diabetes mellitus. One brother living and well. One aunt has pulmonary tuberculosis, one cousin died of pulmonary tuberculosis.

Marital History Married, wife and two children living and well.

Physical Examination General development was good There was no evidence of recent weight loss

Head and Neck No abnormalities noted

Chest No abnormal impulses were seen and the percussion note over the lung areas was normal The apex beat of the heart was just outside of the nipple line, and the percussion outline indicated enlargement of the heart, both to the left and to the right The heart tones were regular and strong A pericardial rub was heard in the third and fourth interspaces to the left of the sternum during systole and diastole The breath sounds were normal and no râles were heard The blood pressure was 130 systolic and 80 diastolic

Abdomen Negative on palpation and percussion

Extremities Negative

Laboratory Data The hemoglobin was 92 per cent, leukocytes 9,500 The urinalysis was negative chemically and microscopically The Wassermann reaction was negative An electrocardiogram showed an auricular and ventricular rate of 80, with a PR interval of 0.14 second, there was a slight elevation of the ST interval, with a beginning downward deflection of the T-wave in the first lead

A tentative diagnosis of pericarditis was made and hospitalization advised

The patient, however, remained at home and symptoms continued to increase until the evening of April 23, when he noted a sudden aggravation of his precordial pain This was followed by marked pallor, weakness and unconsciousness When seen shortly afterwards the heart action was very feeble He had alternating extrasystoles, coming very close to the preceding beat, and insufficiently strong to be recorded in the radial pulse, giving the impression of a marked bradycardia His blood pressure was 80 systolic and 60 diastolic No congestive râles were noted in the lungs, but the liver was slightly enlarged and tender He was brought to St Mary's Hospital, where he remained during the subsequent course of his illness

Shortly after admission to the hospital his temperature was 99°, and varied between this point and 101.8° during the next three weeks, after which the temperature was normal or subnormal up to the time of his death, which occurred on June 16 The heart rate was seldom over 80 beats per minute until the last two weeks, when definite cardiac failure developed The pain continued and the pericardial rub was present, until about two weeks ante mortem

Urinalysis was consistently negative The leukocyte count ranged from 11,800 to 16,000 The differential white count showed a variation from 61 to 81 per cent polymorphonuclears, 14 to 35 per cent lymphocytes, 2 to 4 per cent transitionals, and an average of 1 per cent eosinophiles The hemoglobin ranged between 85 and 93 per cent, and the red blood count from 4,200,000 to 4,670,000

A stereo roentgenogram (figure 1 a) of the chest made on May 11, 1931 indicated a generalized cardiac enlargement, but no evidence of pulmonary or pleural involvement A single roentgenogram (figure 1 b) of the chest made on May 25, 1931 showed that the cardiac outline was slightly larger than that previously noted, and was suggestive of a moderate pericardial effusion The left costophrenic angle was obliterated and there was indication of a thickening of the pleura of the entire left lung

An electrocardiogram (figure 2 a) on May 12, 1931 showed an auricular and ventricular rate of 90 with a PR interval of 0.14 second There was a deep inversion of the T-wave in Leads I and II, with a decreased amplitude of the T-wave in Lead III An electrocardiogram (figure 2 b) on May 23, 1931 revealed an auricular and ventricular rate of 100, with a PR interval of 0.16 second, an elevation of the ST interval in Leads I and II, with a downward deflection of the T-wave in these same leads, and a definite right axis deviation

One consultant suggested a subacute bacterial endocarditis or a tuberculous mediastinitis as the basis for the symptoms presented (A blood culture failed to show any growth and a Mantoux reaction was absent)

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THE HEART IN PULMONARY TUBERCULOSIS, ELECTROCARDIOGRAPHIC CONSIDERATION¹

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THIS report and discussion is based on impressions gained from clinical observation, including a roentgenological and electrocardiographic study, of 416 cases of active tuberculosis and of 44 inactive cases. This series is believed to represent the largest group studied to date. It is unique because the average age of the patients is somewhat higher than is usually found in a sanatorium group. Approximately 25 per cent of the active cases have been observed over a period of two to seven years. During this period of observation, repeated cardiograms and roentgen-rays were made. Circulatory disturbances dominate the clinical symptoms and are the primary cause of death in many instances. Thirty-eight of the active cases showed an arterial hypertension, in 19 of these the hypertension was classed as minimal, in 8 cases moderate, and in 11 cases severe. General arteriosclerosis was noted in 14 of the hypertensive group. Renal lesions of significance were proved in only one instance.

The average age of the 378 cases with normal or subnormal arterial tension was 38.5 years, that of the hypertension group 42 years. Of the hypertension cases 42.1 per cent were in the third decade, 47.4 per cent in the fourth decade, 5.3 per cent in the fifth decade, and 5.2 per cent in the sixth decade of life. The youngest case was 30 years, the oldest 60. A survey of 109 cases of hypertensive heart disease not associated with active tuberculosis diagnosed at this facility showed 22 per cent in the third decade, 37.6 per cent in the fourth decade, 21.1 per cent in the fifth decade, 19.2 per cent in the sixth decade. Matz¹⁴ in a report of study of 330 veterans with heart disease found 59 cases of arteriosclerosis with an average age of 42.7 years and 17 with essential hypertension, average age 35.6 years. White¹⁵

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Study was made at Veterans Administration, Tucson, Arizona.

in a series of 709 cases of hypertensive heart disease found 62 per cent in the sixth and seventh decades while only 21 per cent were under 50 years of age. The pulmonary tuberculosis cases with hypertension show a higher percentage in the third and fourth decades than is indicated in the reports of the non-tuberculous cases. The incidence of arterial hypertension in the cases reported at this time is approximately 8 per cent. Complete cardiovascular examination has been limited to those cases presenting either subjective or objective findings suggesting impairment of cardiac function. The incidence of hypertension in the total number of tuberculous patients treated at this facility has not been determined but probably does not exceed 1 per cent.

Mediastinal distortion resulting in sudden or slow shifting of the heart and great vessels is not an uncommon occurrence in pulmonary tuberculosis. A slowly developed distortion is the result of (1) a unilateral narrowing of the lung field due to slow contraction of extensive fibrotic processes within the lung, (2) contraction of the lung, a sequela of a compressed lung by artificial pneumothorax, the lung becoming cirrhotic and atelectatic as a result, and (3) artificial pneumothorax or hydrothorax of the opposite side. Sudden development of distortion, associated with shifting of heart, is usually due to atelectasis, the result of blocking of a bronchus causing partial or complete collapse of lung, or to pressure from the opposite side as the result of spontaneous pneumothorax.

The shifting of the anatomical position of the heart is a possible cause of the abnormalities of the QRS group of the electrocardiogram, a shift to the left is expected to cause a right axis deviation unless there is a rotation on the anatomical axis sufficient to neutralize the effect of the lateral displacement. A similar though less marked change occurs when the heart is displaced to the right with a tendency to left axis deviation. Experimental work by Meek and Wilson¹ on the dog's heart demonstrated that rotation of the displaced heart on its longitudinal axis materially affected the electrical axis. Elevation of the diaphragm, especially the left, causes a rotation of the heart, thus affecting the electrical axis oppositely from what is expected in many instances. The correlation of electrocardiographic changes in the cases under discussion is given in table 1, A and B. In the 108 cases showing shift of the heart to the left, 26.8 per cent showed right axis deviation, 9.2 per cent left, and 64 per cent none at all. In the 44 cases showing shift of heart to the right, 11.4 per cent showed left axis deviation, 13.6 per cent right, and 75 per cent none at all. In the 226 cases showing no shift 5.8 per cent showed left axis deviation, 12.4 per cent right, and 81.8 per cent none at all. The above group included all cases of active pulmonary tuberculosis, showing normal or subnormal arterial tension. In the group showing arterial hypertension listed in table 1-B, there are three cases recorded as shift of heart to the right, none of which showed axis deviation, 11 cases showed shift to the left, of which 27.2 per cent had

TABLE IA
Active Pulmonary T B (Normal or Subnormal Arterial Tension)

X-R iv		Electrocardiographic Changes																										
		Number of Cases	Normal Ekg	Elec Axis			P-Wave			Q-Wave			Q R-S				S T		I-Wave				Percentage of Total					
				R-Axis Deviation	L-Axis Deviation	No Axis Deviation	Low Voltage	Increased Amplitude	Increased Duration	Q ₁	Q ₂ and ₃	Q ₃	I-V Block	Slurring R or S	Low Voltage	R and S Leads 1-2-3	Elevation	Depression	Low Voltage	Increased Volt —No ST	Inverted I and II	Inverted II and III	Disturbance Rhythm	P-Wave Abnormal	QRS Abnormal	ST Abnormal	T-Wave Abnormal	Q-Wave Abnormal
Shift of heart to R	44	6	5	33	8	2	3	1	0	2	2	9	5	0	2	2	6	5	0	2	11	3	34	36	9	29	6	
Shift of heart to L	108	29	10	69	23	6	9	3	1	5	7	25	8	7	7	3	19	6	0	5	8	38	43	9	27	8		
No shift of heart	226	28	13	185	31	14	22	1	1	3	17	22	11	19	13	9	38	11	3	8	10	31	30	9	26	2		

TABLE IB
Active Pulmonary T B (Arterial Hypertension)

Electrocardiographic Changes

Percentage of Total

Electrocardiographic Criteria																									Percentage of	
X-Ray	Position of Heart	Number of Cases	Normal Ekg	Elec Axis			P-Wave		Q-Wave			Q-R-S			ST		T-Wave					Q-RS Abnormal	ST Abnormal	T-Wave Abnormal	Q-Wave Abnormal	
				R-Axis Deviation	L-Axis Deviation	No Axis Deviation	Low Voltage	Increased Amplitude	Increased Duration	Q ₁	Q ₂ and ₃	Q	I-V Block	Slurring R or S	Low Voltage	R and S Leads 1-2-3	Elevation	Depression	Low Voltage	Increased Volt —No ST	Inverted I and II					Inverted II and III
	Shift of heart to R	3	0	0	0	3	0	1	0	0	0	0	0	0	0	2	1	0	1	0	0	33 3	33 3	66 6	66 6	0
	Shift of heart to L	11	1	3	4	4	2	1	0	0	2	2	0	1	0	0	1	0	1	1	0	27 2	45 4	18	27 2	9
	No shift of heart	24	2	2	8	14	2	5	2	0	2	5	1	0	0	3	5	0	1	2	8 1	37 5	33 3	12 5	37 5	8 1

right axis deviation, 36.4 per cent left, and 36.4 per cent none at all. In the 24 cases showing no shift of the heart, 83.3 per cent showed right axis deviation, 33.3 per cent left, and 58.4 per cent none at all. The criteria as outlined by Pardee⁴ were employed in determining the electrical axis. When the term "axis deviation" is used in this discussion we refer to the electrical axis. When the term "shift" or "shifting of the heart" is used we refer to the anatomical axis.

Brumfiel² made a study of the degree of circulatory embarrassment in cases showing distortion of the mediastinum combined with cardiac displacement. He concluded that there was more pronounced functional impairment in cases of this type than in those showing no displacement.

The writer's observation of cases showing distortion of the mediastinum of a moderate or marked degree, tends to confirm the findings of Brumfiel. Dyspnea, out of proportion to the degree of pulmonary involvement, simple tachycardia, frequently complicated by paroxysmal attacks, a higher percentage of cases presenting the more pronounced evidences of right heart dilatation as manifested by edema of the extremities, hepatic engorgement, and digestive disturbances. Abnormalities of the QRS and T-waves of the electrocardiograms are also more common as will be noted by referring to tables 1-A and 1-B.

A diagnosis of mediastinal distortion, associated with shifting of the heart to the right or left, was made by roentgenological examination in 166 cases or 39.9 per cent of the total number of active cases studied. There was a shift of the heart to the left in 119 instances. Of these 111 were due to contraction of the left lung field and 8 to pneumothorax or hydro-pneumothorax on the right. A shift to the right was found in 47 cases, 39 due to narrowing of the right lung field and 8 to pneumothorax or hydro-pneumothorax on the left.

SYNOPSIS OF CASE HISTORIES

The cases reported have been selected as representing some of the interesting electrocardiographic changes noted in the series.

CASE REPORTS

Case 1 Male, white, aged 37. The history indicates onset of pulmonary tuberculosis in 1918. Negative for luetic infection. No history of anginal syndrome. Figure 1 (top) represents a roentgenogram made December 1931 indicating a far advanced pulmonary tuberculous involvement, moderate contraction of the left lung field with slight shifting of heart and mediastinum to the left. There is also a suggestion of pleuropericardial adhesions in the upper mediastinal area. Blood pressure systolic 84, diastolic 58. Figure 1 (bottom), the electrocardiogram of this patient, presents a Q_1 and a slight prolongation of the PR interval.

Case 2 Male, white, aged 35. The history indicates the onset of pulmonary tuberculosis in 1923. There were pulmonary hemorrhages at about this time. There was no history of luetic infection, and the serologic tests were negative. Figure 2

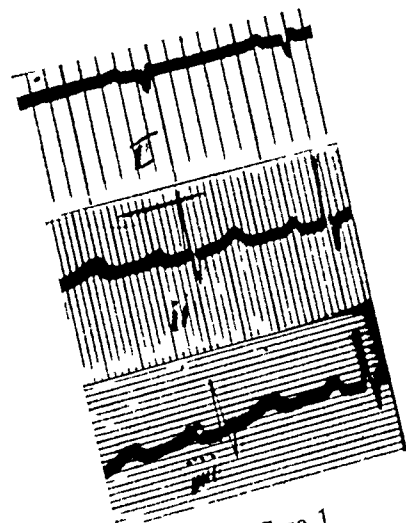


FIG 1 Case 1

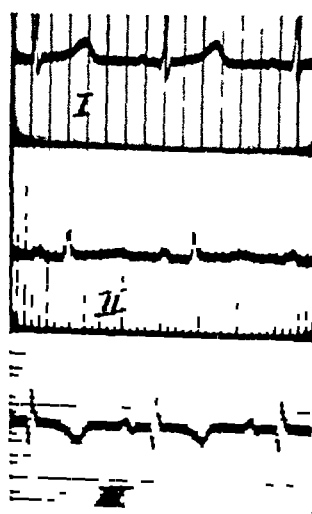
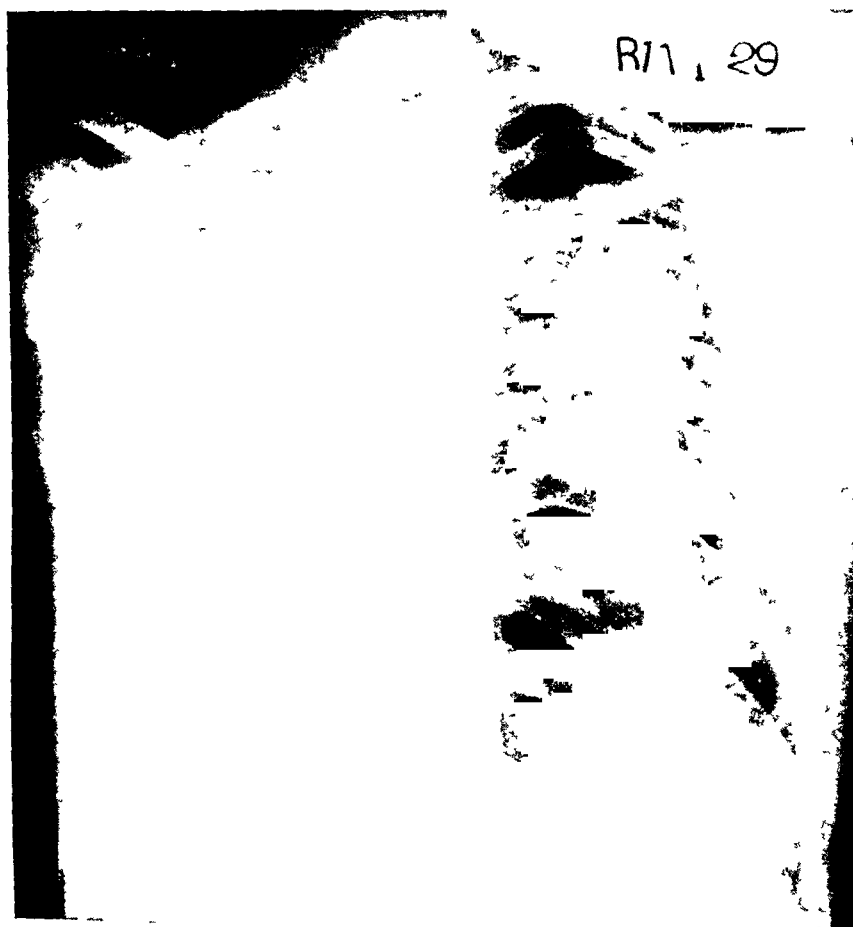


FIG 2 Case 2

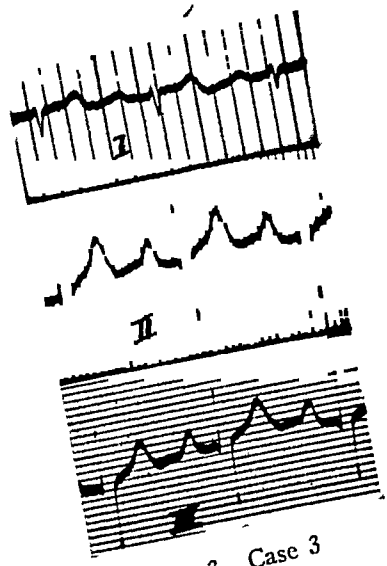
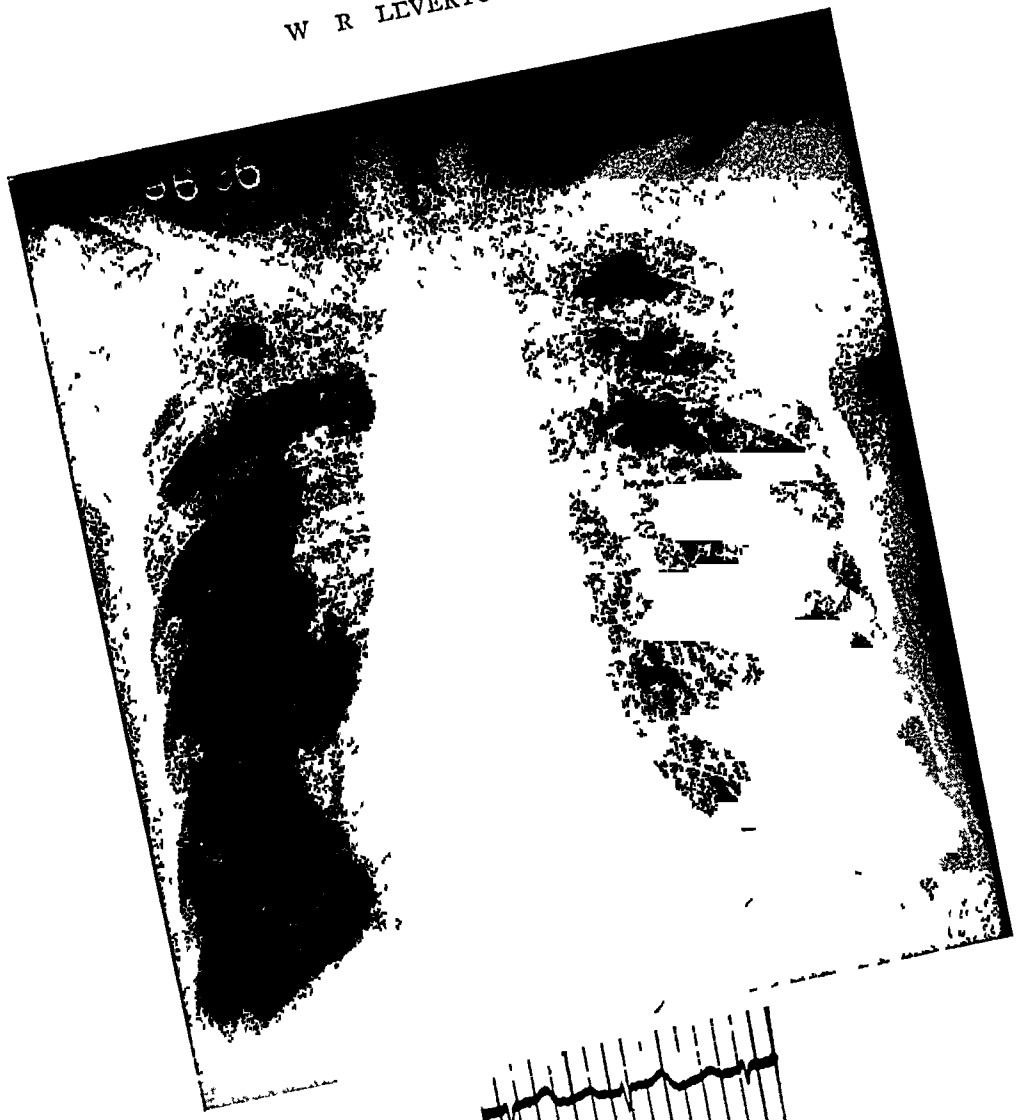


FIG 3 Case 3

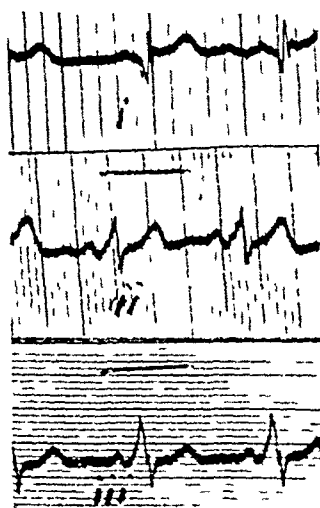


FIG 4 Case 4

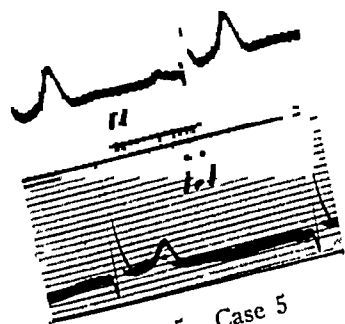
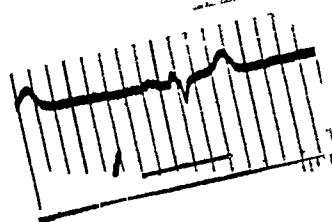


FIG 5 Case 5

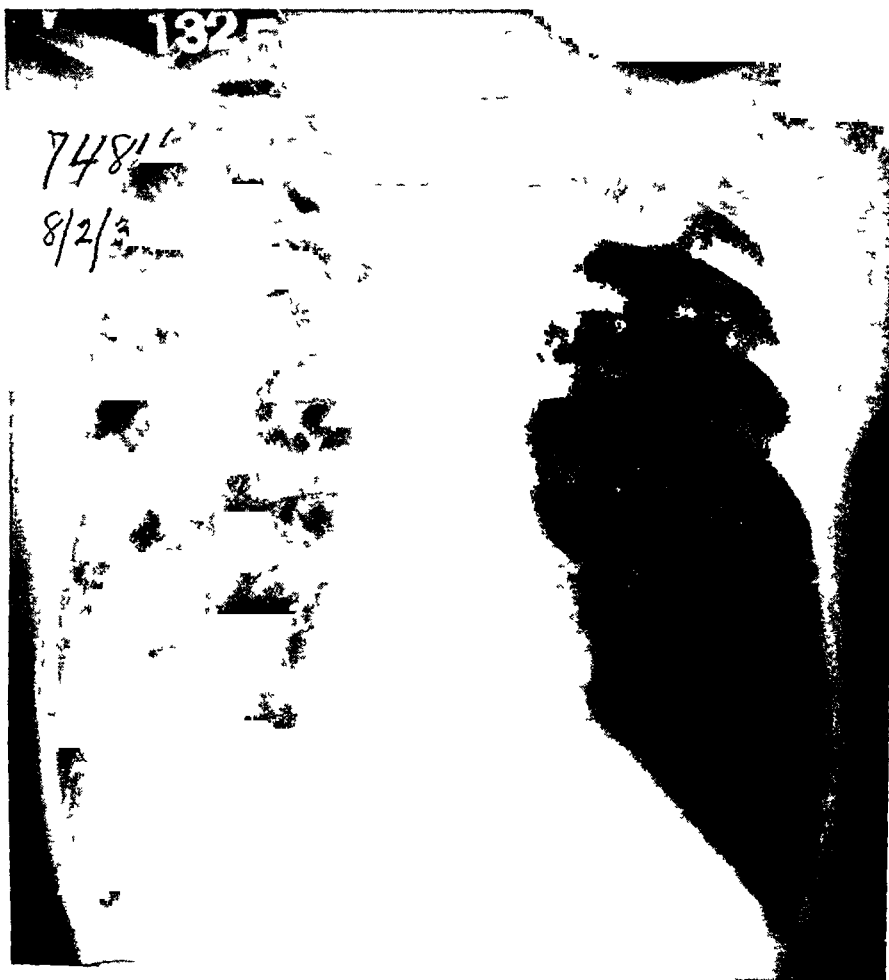


Fig 6 Case 6

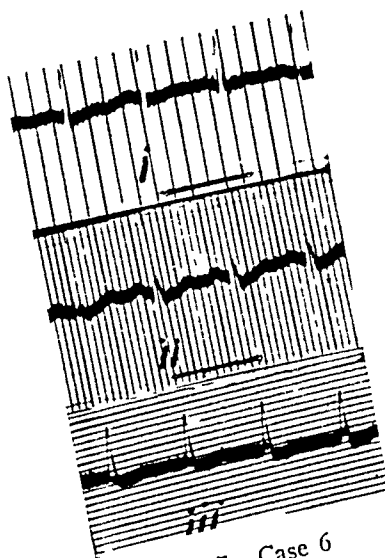


Fig 7 Case 6

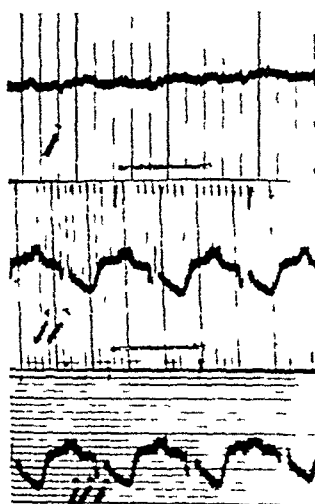


Fig 8 Case 7

(top) represents a roentgenogram made November 1929 indicating extensive tuberculous involvement of the left lung with marked narrowing of the lung field due to massive collapse and marked shifting of heart and mediastinum to the left. Blood pressure systolic 100, diastolic 70. Figure 2 (bottom) represents an electrocardiogram made September 1930 showing a Q_3 with inverted T_1 .

Case 3 Male, white, aged 36. The history places the onset of pulmonary tuberculosis in 1923. No history of luetic infection, blood Wassermann negative. No anginal syndrome. Figure 3 (top) represents roentgenogram made May 1930 indicating an extensive bilateral, active tuberculosis. The heart is in median position but there are indications of pleuropericardial adhesions in the upper mediastinal area. Figure 3 (bottom) shows an electrocardiogram made May 1930. Attention is invited to the high amplitude of P_2 and P_3 , the equal amplitude of R and S in Leads II and III with a rather unusual type of ST_1 and a high amplitude of T_2 and T_3 .

Case 4 Male, white, aged 34. A diagnosis of pulmonary tuberculosis was made in 1918. Phrenic nerve exeresis, permanent, was performed on the left side in 1930. No cardiac pain, but complains of "rapid heart action". Blood pressure systolic 114, diastolic 86. Figure 4 (top) represents roentgenogram made January 1930 which shows far advanced, active lesion, left, fibrotic right, distortion of the mediastinum with shifting of heart to the left, elevation of left diaphragm, and general narrowing of the lung field. Figure 4 (bottom) represents an electrocardiogram made March 1930 which shows a Q_1 , slurring of R, elevation of RST_1 , and intraventricular block. This patient left the hospital in 1930 and died March 16, 1932 in another institution. No congestive failure or symptoms indicating increased impairment of cardiac function were noted. Postmortem findings were as follows:

- 1 Peritonitis, acute, general, due to acute suppurative appendicitis, with rupture
- 2 Appendectomy, recent
- 3 Tuberculosis, pulmonary, chronic, apex right and both lobes left
- 4 Pleurisy, tuberculous, chronic, fibrous, adhesive, over all lobes, bilateral, right slight, left marked
- 5 Diaphragmatic and pericardial adhesions, bilateral, right slight, left marked
- 6 Dilatation, cardiac, concentric
- 7 No demonstrable coronary disease

Case 5 Male, white, aged 36, diagnosed pulmonary tuberculosis in 1928. "Pleurisy pain" left lower chest. Paracentesis left chest in 1928, presumably for pleural effusion. Blood pressure systolic 110, diastolic 70. Figure 5 (top) represents a roentgenogram which shows narrowing of the left lung field, thickened pleura left lower, apparent elevation of the left diaphragm, and cavitation in right upper. Figure 5 (bottom), the electrocardiogram made February 1930, shows low voltage of P, increased duration of QRS interval (intraventricular block), slurring of R, and elevation of RST_2 and T_3 .

Case 6 Male, white, aged 43. The diagnosis of pulmonary tuberculosis was made in 1928. There was a history of chancre about 1910. No collapse-therapy. Blood pressure systolic 106, diastolic 70. There are no physical findings suggestive of a cardiovascular syphilis. Figure 6 (top) represents a roentgenogram made August 2, 1935, which shows a bilateral, active tuberculous lesion, with cavitation in the right upper, heart in the median position, of the small asthenic type. Figure 6 (bottom) reproduces an electrocardiogram made August 10, 1935, which shows no abnormality of importance. On November 15 the patient complained of sudden onset of dyspnea and weakness. Figure 7 (top) represents a roentgenogram made November 15, 1935, which shows opacity of the right lung, and the mediastinum distorted with shifting of the heart to the right. Diagnosis: Acute atelectasis right lung, due to sudden blocking of the bronchus. Figure 7 (bottom) reproduces a



FIG 9 Case 8

cardiogram made on the same day. Note the change in voltage of T and the depression of RST, and Δ . This cardiogram is not unlike the EKG with staircase ST recorded by McGinn and White,¹³ associated with acute *cor pulmonale*. This case terminated in death some two months later. No post mortem was permitted.

Case 7 Male, white, aged 51. The onset of tuberculosis was in 1928. The history is negative for anginal syndrome. No arteriosclerosis is demonstrable. The systolic blood pressure was 118 and the diastolic 80. Figure 8 (top) represents a roentgenogram made September 1932, which shows bilateral, active tuberculosis with extensive cavitation, the heart of the asthenic type, and in median position. There is a suggestion of adhesions around the base of the heart. Figure 8 (bottom) reproduces an electrocardiogram made September 1932. There is pronounced disturbance in RST₂ and Δ , with inverted T₁ and Δ . (No digitalis). The present status of this patient is unknown.

Case 8 Male, white, aged 44. The onset of pulmonary tuberculosis was in 1918. Pneumothorax was induced on the right in 1922 and continued until about 1930. There is no record of blood pressure prior to December 1932, date of first cardiovascular examination. The systolic blood pressure was then 226 and the diastolic 150. Figure 9 (top) represents a roentgenogram made December 1935. It shows no change of importance from that taken in 1932. There is marked contraction of the right lung field with distortion of the mediastinum and shifting of heart to the right. The distortion is presumably the result of contracted lung, massive atelectasis, a sequela of compressed lung from long-continued pneumothorax. Figure 9 (bottom) represents an electrocardiogram made December 1935 and is very similar to the record of December 1932. There is depression of the RST and inverted T₁ and Δ . The electrocardiographic changes are not unlike those frequently observed in hypertensive heart disease although there is no roentgenological evidence of cardiac enlargement.

DISCUSSION

The QRS, RST, and T-waves are subject to many variations caused by change of potential within the heart muscle. Factors responsible for such changes in the QRS group, according to Paidee,³ are (1) The normal variations in the structure and distribution of the terminal arborizations of the auriculoventricular bundle inside the two ventricles. (2) Position of the heart within the thorax. (3) The relation of the weight of the muscle masses of the right and left ventricles. The RST segment and T-wave show normal variations depending on the changes in electrical potential resulting from the degree of change in position of the heart during systole, and the variation in the rate of relaxation of the ventricular muscle.

The presence of Q_1 is considered as indicating coronary disease when "it measures at least 1 mm and is at least $\frac{1}{3}$ as large as the largest R deflection in any lead, and in which there is a definite R-wave in Lead I measuring less than 5 mm in amplitude." Paidee⁴ has recognized the Q_1 as indicative of coronary disease when it measures 25 per cent or more of the largest amplitude of the QRS shown in any one lead. Twelve of the 416 cardiograms studied show a Q_1 which conforms to the standards set forth by Paidee.⁴ Two of these patients were obese, with high diaphragms¹¹, five showed an elevation of the left diaphragm associated with

narrowing of the left lung field, and pleural thickening, one case showed an elevation of the right diaphragm secondary to phrenic nerve evulsion, one case, arterial hypertension, one case, a progressive tuberculous lesion with extensive cavitation showed only a transitory Q_3 , the remaining two cases had possible mediastinal adhesions. There were two cases that showed a Q_2 and Q_3 which conform to the standards outlined by Durant⁵, one of these showed quite pronounced coronary sclerosis at post mortem. There was no autopsy in the other case. None of these patients presented symptoms suggestive of an anginal syndrome. The question is raised as to the influence of change in position of the heart upon the occurrence of Q waves, especially in those patients presenting definite evidence of elevation of the diaphragm.

Electrocardiograms of the Q_1 type conforming to the standards as set forth by Durant⁵ were found in five instances. Three of these occurred in cases showing definite shifting of the heart to the left, one in shift to the right, and one in no shift. None of these cases presented a typical anginal syndrome, and the cause for the Q_1 was undetermined.

Slurring or notching of R or S with no increase in the QRS interval was noted in 56 or 15 per cent of the normal and subnormal arterial tension cases, and in eight or 20 per cent of the hypertension cases. There are 27 records which show the R- and S-waves approximately equal in amplitude in two leads with an R and S present in the third lead¹². Pardee⁶ called attention to this peculiarity and advanced an opinion that such an arrangement does not occur in records from normal hearts. An opinion from the author as to the pathological significance would be of little value. It is believed to indicate myocardial disturbance of some type.

Thirty graphic records in this series, 7.2 per cent, are tabulated as indicating intraventricular block. Only three of these cases showed a typical bundle-branch block, two left and one right. In 13 of this group the electrocardiograms appear to meet the requirements for atypical bundle-branch lesions as outlined by Dr. Henry T. von Deesten and Dr. Moses Dolganos while 14 of them show an increased duration of the QRS interval without the prolonged notched S-wave. The average age of patients in this group of intraventricular block was 39.4 years. Considering the age, this appears to be a rather high percentage of disturbance in intraventricular conduction. The increased duration of the QRS indicates a delay in the spreading of the contraction waves over the ventricles. In the typical bundle-branch lesions it is believed that the delay in spreading of the contraction wave is due to the necessity of the conduction impulse to spread from one ventricle to the other instead of simultaneously spreading through the right and left branches of the bundle. The atypical bundle-branch block is also indicative of serious myocardial damage causing a disturbance in conduction. The increased duration of the QRS interval without associated abnormality as found in bundle-branch lesions, is not believed to be due to thickening of ven-

tricular muscle because in these tuberculous cases there is little if any evidence of ventricular hypertrophy. Wilson and Herman⁸ expressed the opinion that the increased duration of the QRS was not always due to increased thickness of the ventricular wall. The clinical picture in this series of cases, regardless of the degree of disturbance in the QRS, was very similar. In one of the cases classified as typical bundle-branch block, there was a history of an anginal attack which may have been due to coronary thrombosis. The history was negative for the anginal syndrome in the other two cases. In one case with an atypical record the postmortem findings showed a definite coronary sclerosis. The history suggests a possible anginal syndrome in two cases, but was negative in all others. In those cases showing a simple increase in duration of the QRS interval there were two with subjective symptoms of angina. It seems reasonable to assume that the disturbance of conduction may be accounted for by a disturbance of the circulation in the bundle-branch tissues.

Electrocardiograms of 43 cases, 10.3 per cent, were recorded as showing abnormalities of the RST segment. Pardee first called attention to inversion of the T deflection and also to the associated changes of the RST segments in coronary thrombosis. Parkinson and Bedford⁹ discussed the characteristic serial changes in the RST segment and the T-wave, and classified them as of T_1 and T_3 type. In our series there was only one case presenting the T_1 type, and none the T_3 type. One case showed elevation of RST_2 , associated with inverted $T_{1,2}$ and $_3$, one case, depression of RST_2 and $_3$ with inversion of T_2 and $_3$. In all other instances there was simple elevation or depression of RST without associated inversion of the T. Ten showed depression of RST_2 and $_3$, 12 elevation of RST_2 and $_3$, five elevation of RST_2 , two depression of RST_2 , one elevation of RST_1 , and one elevation of RST_3 .

Graybiel and Paul White¹⁰ in their discussion of the inversion of the T-wave in Lead I or II of the electrocardiogram in young individuals, with neurocirculatory asthenia, with thyrotoxicosis, in relation to certain infections, and following paroxysmal ventricular tachycardia state "The T-wave is much less stable than the other electrocardiographic deflections. Although its mechanism is obscure, we are familiar with certain secondary factors which may change its form and direction. Chief among these are alterations of coronary circulation, disturbances of nervous origin, the action of toxins or drugs, and change in the position of the heart." In this series, we have tabulated six records showing inversion of T in Leads I and II, and 18 showing inversion of T_2 and $_3$. There were 70 records showing low voltage of T. In this group, we considered the low voltage of T only when the T-wave showed an amplitude of less than one millimeter in all leads. It is difficult to evaluate the significance of this abnormality of the T. The far advanced terminal cases presenting the usual evidence of nutritional disturbance, with extensive pulmonary lesion, in many instances

show low voltage of T, however, this is not universally true. A number of cases were observed which were of the well nourished ambulant type with a moderate degree of pulmonary involvement which showed a low voltage of T at all times. It appears, therefore, that the low voltage T is not a positive indication of myocardial weakness, and should be considered only in connection with abnormalities of the QRS group.

SUMMARY

The electrocardiogram of 189 hearts, 45.5 per cent of the total number of active pulmonary tuberculosis cases studied, showed significant changes in the QRS, RST, or T deflections. Included in the eight case reports presented, there is a Q_1 which appears to meet the requirements set forth by Durant⁷ as an indication of coronary disturbance, a Q_s measuring 25 per cent or more of the largest deflection of the QRS shown in any one lead suggested by Pardee⁴ as indicating coronary disease, another record showing an R and S of approximately equal amplitude in two leads with predominant S_1 and an abnormal ST_2 and $_3$. The fourth case shows, in addition to Q_1 , an intraventricular block. The next case shows an increased duration of the QRS with an elevated RST_1 and $_2$. The sixth case is especially interesting because the record is practically normal until the patient suffered a sudden spontaneous atelectasis which caused a shifting of the heart to the right. The record made subsequent to this accident showed a flattening of the T in all leads, also a depressed RST_2 and $_3$. The "staircase" ST in this cardiogram is not unlike those recorded by McGinn and White¹³ associated with acute *cor pulmonale*. The record of the next case appears a bit unusual in the absence of a clinical picture of coronary disturbance or evidence of cardiac enlargement. Case 8 is one of severe arterial hypertension showing a not unusual picture of depressed RST_2 and $_3$ in conjunction with an inverted T in the same leads. The interesting feature in this case is the marked distortion of the mediastinum, secondary to contraction of the right lung (atelectatic). This patient is living and presents the usual picture of hypertensive disease. It is interesting to speculate on the relation of the cardiac displacement to the hypertension.

The average age in this group of cases is probably higher than in any known group previously reported. The average duration of the pulmonary lesion, not possible to compute accurately, is estimated at approximately 15 years. So it may be said that these men are naturally approaching the "heart age". Interesting electrocardiographic changes, however, have been observed in patients between 30 and 35 years of age.

It is suggested that the abnormalities of the QRS, RST, and T-waves noted in a large percentage of this group may be due to a chronic nutritional disturbance of the myocardium incident to pulmonary tuberculosis, that there is present in the soft, flabby heart a deficiency of the coronary circulation resulting in an impairment of conduction similar to the disturbance

caused by coronary sclerosis. Dilatation and associated hypertrophy of the right heart, directly the result of the long-continued strain due to increased pulmonary resistance, may be responsible for changes in the RST segment or T-wave. There are other factors such as cardiac displacement, pleuropericardial adhesions, tuberculous pericarditis, elevation of one diaphragm, and possibly other anatomical or pathological changes which cannot be overlooked as contributing or causative agencies. The cause of these electrocardiographic changes in pulmonary tuberculosis has not been proved. The subject apparently deserves further investigation.

CONCLUSIONS

1 Four hundred and sixteen cases of active pulmonary tuberculosis and 44 inactive were studied. The cases were classified according to anatomical position of the heart, 47 showed shift of the heart to the right, 119 to the left, and 250 no shift of heart.

2 Thirty-eight of the active cases showed an arterial hypertension, none of the inactive cases.

3 One hundred and eighty-nine, or 45.5 per cent of the total number of active cases studied showed significant changes in the QRS complex, the RST segment or the T-wave. None of the inactive cases showed any important abnormality of the electrocardiogram.

4 There were 19 graphic records which showed an abnormal Q-wave, 12 of these of the Q_s type described by Pardee. Thirty cases showed intraventricular block, 43 abnormality of the RST segment, and 119 abnormal T-waves.

5 The electrical axis is apparently influenced by the rotation of the heart on its longitudinal axis.

6 The percentage of cases showing an increase in the duration of the QRS depression and elevation of the RST with T-wave changes is higher than expected and suggests that the nutritional disturbance of the myocardium found in pulmonary tuberculosis of long standing may produce a similar electrocardiographic picture to that found in coronary disease.

7 The electrocardiogram is of value in the diagnosis of cardiac lesions associated with pulmonary tuberculosis. It is frequently the only positive evidence of myocardial disturbance.

REFERENCES

- 1 MEEK, W J, and WILSON, A. The effect of changes in the position of the heart on the QRS complex of the electrocardiogram, *Arch Int Med*, 1925, *xxxi*, 614.
- 2 BRUMFIEL, D E. The heart in tuberculosis, *Am Rev Tuberc*, 1933, *xxviii*, 317.
- 3 PARDEE, H E B. The significance of an electrocardiogram with a large Q-wave in Lead III, *Arch Int Med*, 1930, *xlvi*, 470.
- 4 PARDEE, H E B. *Clinical aspects of the electrocardiogram*, third edition, 1933, Paul Hoeber, Inc.
- 5 DURANT, T M. The initial ventricular deflection of the electrocardiogram in coronary disease, *Am Jr Med Sci*, 1934, *clxxxviii*, 225.

- 6 PARDEE, H E B Personal communication
- 7 VON DEESTEN, T T, and DOLGANOS, M Atypical bundle-branch block with favorable prognosis, *Am Jr Med Sci*, 1934, *clxxxviii*, 231
- 8 WILSON, F N, and HERMAN, G R An experimental study of incomplete bundle branch block and the refractory period of the heart in dog, *Heart*, 1921, *viii*, 229
- 9 PARKINSON, J, and BEDFORD, D E Successive changes in the electrocardiogram after cardiac infarction, *Heart*, 1928, *xiv*, 195
- 10 GRAYBIEL, A, and WHITE, P D Inversion of the T-wave in Lead I or II of the electrocardiogram in young individuals with neurocirculatory asthenia, with thyrotoxicosis, in relation to certain infections, and following paroxysmal ventricular tachycardia, *Am Jr Med Sci*, 1935, *x*, 345
- 11 PARDEE, H E B The significance of an electrocardiogram with a large Q-wave in Lead III, *Arch Int Med*, 1930, *xlvi*, 470
- 12 PROGER, S H, and MINICH, W R Left axis deviation with and without heart disease, *Am Jr Med Sci*, 1935, *clxxxix*, 674
- 13 MCGINN and WHITE, P D The acute cor pulmonale, *ANN INT MED*, 1935, *ix*, 115
- 14 MATZ, P B A study of heart disease among veterans, *New England Jr Med*, 1935, *ccxii*, 929
- 15 WHITE, P D Heart disease, 1931, The Macmillan Co, New York

COMMON GASTROINTESTINAL EMERGENCIES AND THEIR MEDICAL ASPECTS

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DISEASES or disorders which may give rise to gastrointestinal disturbances of sufficient gravity to constitute an emergency may be roughly classified as follows: (1) acute inflammatory diseases of the abdominal viscera and their complications, such as peritonitis, obstruction, intussusception, torsion, perforation and abscess formation, (2) complications involving chronic lesions, especially of the upper part of the digestive tract, the most important of these are acute perforation, obstruction and hemorrhage, (3) disease or dysfunction of extra-abdominal organs in which the symptoms are predominantly of gastrointestinal nature, and (4) complications which arise during treatment or follow operation and which are chiefly toxic or mechanical in nature.

In a consideration of the various entities comprised in this classification the rôle of the physician is especially important not only in the diagnosis but in the treatment of the emergency states, whether independently or in collaboration with the surgeon.

THE "ACUTE SURGICAL ABDOMEN"

Symptoms usually characteristic of a gastrointestinal emergency are severe abdominal pain, protracted vomiting or diarrhea, massive hemorrhage, painful distention with or without visible peristalsis, or a variable combination of these symptoms. Prostration, shock, tetany, and even delirium and coma may coexist or supervene.

As the physician is usually the first to see the patient, upon him is placed the grave responsibility of as prompt and accurate an appraisal of the situation as circumstances permit, and of securing without delay surgical consultation when it is indicated or when any reasonable doubt exists. The physician must be as mindful as the surgeon of the rapidity with which disastrous changes can occur in the abdomen and of the factor of delay or indecision, which too frequently allows an acute abdominal emergency to become an abdominal disaster. Severe pain of gradual or sudden onset usually dominates the picture. When this is associated in whole or in part with such significant signs and symptoms as localized tenderness, muscular rigidity, distention, nausea and vomiting, leukocytosis and fever, the situation is one that usually requires prompt surgical intervention.

The nature of such lesions and their diagnostic and surgical aspects

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recently have been summarized in an instructive article by Abell. With such lesions, exclusive of their diagnostic aspects and symptomatic and supportive treatment, we, as physicians, are not so directly concerned. Possibly, exception may be taken in three instances: (1) that form of subacute (protected, *forme fruste*) type of perforated ulcer which, at the outset, closely simulates acute perforation, in nature, if not in degree, but from which the patient usually recovers without surgical interference, (2) those instances of acute gastritis or gastro-enteritis which also may simulate acute perforation of an ulcer and acute appendicitis, as has been emphasized recently by Klostermeyer and by Dietrich, and (3) acute pancreatitis, in which the mortality following operation appears to be considerably higher than that following conservative measures, as has been pointed out by a number of observers in recent years.

When the nature of an acute abdominal seizure has not been determined, it is the universal custom to withhold opiates until one reaches the decision that operation is contraindicated or is to be temporarily postponed. Guerri's statement that "morphine puts two people to sleep, the patient on the one hand and the doctor on the other" tersely expresses the reason for such custom.

By and large, this is probably the safest procedure to follow if suffering and shock are not too great. On the other hand, such a competent and experienced internist as the late Harry Singer, on the basis of observations made by Hildebrandt and Zierold, advocated the *intravenous* administration of $\frac{1}{4}$ gram (0.016 gm) of morphine sulfate or $\frac{1}{20}$ grain (0.003 gm) of dilaudid, if, on account of the severity of the pain, it is difficult or impossible to secure the patient's cooperation in obtaining a satisfactory history or in making a proper physical examination. However, before morphine or dilaudid is given, a sketchy anamnesis is obtained, a preliminary physical examination is made, and the *observations are recorded*. After administration of morphine or dilaudid in such a manner, relief is prompt, the abdomen is relaxed, and the hyperesthesia is more or less eliminated. With a fair degree of accuracy the examiner can then determine (1) the location of the point of maximal tenderness, (2) the degree of tenderness, and (3) the presence or absence of any abdominal mass. Observations made before and after morphine has been administered then can be reviewed. Suffering, exhaustion, and shock are greatly reduced and this renders the patient a better operative risk than he otherwise would be.

This method has much to commend it and although it has certain disadvantages they are by no means insurmountable. When the patient is relieved he may decline to undergo a laparotomy or may suggest that it be delayed. Therefore, the patient or his relatives must be informed of the selective action of the opiate on the pain and of its failure to influence the course of the disease. Also in the presence of a mechanical obstruction, the very active peristalsis heard synchronously with the height of the paroxysm of pain may disappear. But, by reciting to information re-

coided prior to administration of the opiate, the physician will not be deprived of any useful data. Such at least is the opinion of those who advise that morphine should be given intravenously early in the period during which diagnosis is being attempted.

EMERGENCY STATES IN THE COURSE OF A CHRONIC LESION OF THE UPPER PART OF THE DIGESTIVE TRACT

Obviously, symptoms of sufficient gravity to assume the proportion of an emergency in the presence of a chronic abdominal visceral lesion are largely the result of such common complications as acute perforation, hemorrhage, and obstruction. Acute hepatic insufficiency, hemorrhagic diathesis, and circulatory collapse following abdominal paracentesis may somewhat less frequently constitute emergencies, complicating the course of disease of the biliary system.

Acute Perforation An ulcerating lesion of the stomach or duodenum which undergoes acute perforation usually is chronic, it is the perforation that constitutes the acute process. In such cases this complication could logically be included in the group of acute abdomens already discussed. Perforations occur two or three times more frequently among men than among women. While chronic perforation of long-standing lesions is a common complication, acute perforation occurs in only approximately 5 per cent of the cases. Such lesions are usually situated on the unprotected anterosuperior wall of the stomach or duodenum near the pylorus. Although acute perforation occurs less frequently than does hemorrhage or pyloric obstruction, it is the most frequent cause of death, followed by hemorrhage and obstruction in the order named. Evidence of a pre-existing ulcer often makes possible successful recognition of this catastrophe. Graham regarded three symptoms as indicative of perforation: (1) association of pain and tenderness, (2) one point of maximal tenderness, and (3) aggravation of distress on turning over. In questionable cases an ordinary exposure to roentgen-rays centered on the dome of the diaphragm usually will reveal small collections of gas. In the differential diagnosis one must, of course, consider acute appendicitis, acute hemorrhagic pancreatitis, and acute coronary occlusion. The treatment of acute perforation is always surgical and the mortality rate should not exceed 5 per cent if operation is performed within eight hours after perforation has occurred.

Massive Hemorrhage Massive hematemesis or melena, or both, which have their origin in gastroduodenal ulceration, are the cause of death of 13 to 30 per cent of patients who are admitted to large charity hospitals because of such hemorrhage. In general practice it is estimated that the mortality rate does not exceed 3 per cent. The incidence of death during or following the first hemorrhage of severe proportions ranges from 9 to 15 per cent. Duodenal ulcer is the commonest source of such hemorrhages, although the tendency to bleed is associated more markedly with gastric ulcer which,

however, is encountered clinically 10 times less frequently than the former. Other less frequent sources of massive hemorrhage are anastomotic (jejunal) ulcer, carcinomatous gastric ulcer, chronic hypertrophic gastritis, benign neoplasm of the stomach or small intestine, ulcer in a Meckel's diverticulum, and ruptured varices in the lower part of the esophagus or in the stomach which are associated with portal cirrhosis or splenic anemia.

Authorities generally are agreed that age is the greatest factor affecting prognosis. Postmortem findings in the majority of the fatal cases reveal erosion of a sclerosed vessel in the base of a chronic penetrating, or perforated, indurated ulcer, usually on the posterior wall of the duodenum or on the lesser curvature and posterior wall of the stomach. While treatment of profuse hemorrhage is chiefly of a medical nature, it is my opinion that the middle-aged or elderly patient who harbors a chronic lesion should be submitted to operation without unnecessary delay if he has bled on previous occasions, if he does not respond favorably to adequate treatment, as indicated by blood pressure, pulse rate, concentration of hemoglobin, erythrocyte count, and concentration of blood urea (all estimated at stated intervals), and if, in addition, he shows signs of shock, or if hemorrhage recurs at short intervals in spite of such treatment.

The profession is by no means in accord as to the best methods of treatment. There are those who stress the importance of avoiding dislodgment of the clot, they are strenuously opposed to phlebotomy, early feedings, gastric lavage for any reason, and intubation. Others stress the importance of avoiding digestion of the clot, or counteracting hemorrhagic shock, therefore, transfusions, continuous drip treatment and feedings at early and frequent intervals are advocated. In my experience the time honored custom of administering opiates, preferably dilaudid with atropine, hypodermically, the transfusion of 250 cc of blood at frequent intervals, the application of a partly filled ice bag to the abdomen, and the usual measures directed to the treatment of shock, if present, has proved the most satisfactory procedure. However, the consistent, good results attending the use of Witts' modification of the Meulengracht method of early and frequent feedings have influenced us to shorten considerably the period of enforced abstinence from food in these cases.

In recent years, a number of observers have pointed out that massive intraintestinal hemorrhage gives rise to certain derangement in the functions of the organism, which is characterized chiefly by marked elevation of the value for the blood urea (extrarenal uremia), a decrease or cessation of excretion of sodium chloride in the urine, urobilinuria, and a decrease in the concentration of serum protein. Increase in the concentration of blood urea is the most constant symptom, it appears within a few hours following the hemorrhage and persists for a variable period. In spite of the achloruria, the concentration of plasma chlorides may be normal or even increased. The mechanism underlying this phenomenon is still a matter of dispute. When the greater part of the blood is vomited and little reaches

the intestinal tract, these biochemical changes do not occur, thus, the presence of blood in the intestinal canal is an essential prerequisite for development of the increased concentration of blood urea. Christiansen is convinced that these changes, when present, have definite prognostic and therapeutic implications.

High Intestinal Obstruction Undue retention of gastric contents as the result of mechanical hindrance at the pyloric outlet from inflammatory, cicatricial, or neoplastic gastroduodenal lesions, or as the result of motor impairment of the gastric musculature in the presence of lesions which cause only partial occlusion is a common complication. At least, in cases in which the condition has been verified surgically, actual obstruction or gross impairment of emptying of the stomach occurs in from 26 to 30 per cent of cases of benign lesions of the stomach or duodenum and in from 41 to 54 per cent of cases of gastric carcinoma. Cicatricial and neoplastic obstructions are unyielding but obstruction of an inflammatory nature is frequently relieved by proper treatment.

As nausea and vomiting, dehydration and prostration of emergency proportions are common to a wide variety of disorders, as will be shown, too much reliance cannot be placed upon these signs per se in the diagnosis of obstruction. However, vomitus that is suggestive of retention, visible gastric or intestinal peristalsis, undue retention of a barium meal in the absence of migraine or the inhibitory effects of morphine, are trustworthy signs of obstruction. Roentgenologic examination frequently determines the level of the obstruction and its nature. One should remember that rather high-grade obstruction or motor dysfunction may be present in the absence of vomiting, and that on the other hand, marked vomiting may be present in one clinical variant of nonobstructing duodenal ulcer (*ulcus à forme tabétique*), usually to the exclusion of all other symptoms and signs characteristic of the disease.

It is now a matter of common knowledge that a severe, even fatal, toxemia frequently occurs in association with a marked or long-standing high intestinal obstruction. In such cases timely recognition and correction of the toxemia has done far more to reduce surgical mortality in the past 15 years than has any other single procedure. As this, or somewhat similar intoxication occurs in a wide variety of conditions, the subject will presently be discussed at greater length.

EMERGENCY STATES IN THE COURSE OF DISEASE OF EXTRA-ABDOMINAL ORGANS

The extra-abdominal causes of severe abdominal pain, nausea, vomiting, and diarrhea are legion and no one is more aware of that fact than the experienced internist who has perspective and a background of broad training. In the hope of reducing diagnostic error to a minimum, certain procedures compatible even with an emergency can be carried out, namely (1) ap-

praising the evidence deduced from the immediate history, complete physical examination, temperature, pulse rate, blood pressure, leukocyte count, and chemical and microscopic examination of the urine, (2) obtaining details of habits, previous illness, and symptoms antecedent to the present acute illness, (3) carrying out with dispatch certain biochemical, serologic, electrocardiographic, or roentgenologic examinations in the presence of atypical or complicated conditions. Fortunately, the first two procedures supply the necessary information for adequate diagnosis of the majority of abdominal emergencies.

Pneumonia Abdominal pain and increased tension of the upper portion of the rectus and oblique muscles, which occasionally are associated with lobar pneumonia or with pneumonia that involves a lower lobe that is complicated by diaphragmatic pleurisy, may be mistaken for acute appendicitis, especially among children. Such conditions among adults may excite suspicion of leaking duodenal ulcer or acute cholecystitis. Mistakes can be avoided by repeated physical examination and by roentgenologic examination of the lungs whenever necessary.

Angina Pectoris and Acute Coronary Occlusion The occasional epigastric situation of the severe paroxysmal pain of angina pectoris, and the severe oppression or agonizing pain of sudden coronary occlusion is often difficult to distinguish from the pain of perforated ulcer, biliary colic, acute pancreatitis, or mesenteric infarction.

Helpful in differentiation of these conditions, briefly stated, are the following features: (1) the nature of the antecedent history and of the symptoms and signs observed during a seizure, (2) the age and sex of the patient, the vast majority of the victims of coronary accidents are middle-aged or elderly men, (3) the nature of the electrocardiographic, cholecystographic and roentgenographic findings. Sometimes the coexistence of a lesion in the thorax and in the abdomen adds to the diagnostic perplexities. Willius has pointed out, for example, the frequent coexistence of coronary disease with disease of the biliary tract, both of which contribute to the symptoms and signs presented.

Pelvic Disease In the reproductive period of life acute abdominal pain may be the result of ruptured ectopic pregnancy, acute pelvic peritonitis, or rupture or torsion of an ovarian cyst.

EMERGENCIES ASSOCIATED WITH DISEASE OF SOME OF THE DUCTLESS GLANDS

Diabetic Acidosis and Coma Abdominal pain, gastrointestinal disturbances, fever and leukocytosis are present in about 75 per cent of cases of diabetic acidosis before coma supervenes, according to the observations of Bothe and Beardwood. Vomiting by a known diabetic is always of serious import and should never go unheeded. When in doubt, tests for urinary sugar can be carried out in the home, and for diacetic acid with

ferric chloride. If coma threatens or supervenes, prompt intravenous administration of insulin and physiologic saline solution to replace excessive loss of fluids and electrolytes is indicated, because the promptness with which treatment is carried out is one of the most important factors in prognosis. As soon as possible, the patient should be transferred to the hospital where the important determinations of blood sugar and carbon dioxide combining power of the plasma can be made from time to time and adequate therapeutic procedures instituted.

Hypoglycemia In this condition, whether induced or spontaneous, hunger, nausea and vomiting may be prominent symptoms. In certain instances upper abdominal pain is present. This condition is usually encountered among diabetic patients who have taken too much insulin, but the cases of spontaneous origin are more apt to give rise to diagnostic difficulties. Emergency measures consist of the administration of a solution of dextrose, it may be given by mouth in milder cases but if the patient is comatose it should be given intravenously. If a sterile solution is not available a dilution of common corn syrup may be given by stomach tube.

Acute Adrenal Insufficiency This so-called Addisonian crisis is relatively uncommon but is an exceedingly dangerous state of affairs. Such a crisis may be difficult to recognize if the symptoms and signs characteristic of Addison's disease (buccal pigmentation, hypotension, asthenia) are not prominent. Nausea, vomiting, and abdominal pain are striking early symptoms. There are marked changes in the physiochemical constituents of the blood, such as anhydremia, increase in blood urea and nonprotein nitrogen, marked reduction in the values for total base, plasma chlorides and serum sodium, and an increase in the concentration of serum potassium. The treatment consists of the administration of potent extracts of adrenal cortex, the injection of physiologic saline solution to which has been added sodium citrate or a similar sodium salt, and a diet that is low in potassium.

Crisis of Exophthalmic Goiter Anorexia, diarrhea and protracted vomiting, along with restlessness and psychic disturbances, are the chief features of this crisis. If the usual signs and symptoms of exophthalmic goiter are not prominent, the cause underlying the marked gastrointestinal disturbances may be misinterpreted. Laboratory studies furnish little assistance. The treatment consists of frequent repeated doses of compound solution of iodine (Lugol's solution), as much as 10 minims (0.6 cc) every 15 to 30 minutes, taken in milk, grape juice or water, during the first 24 hours, and 30 minims (2 cc) daily thereafter for three or four weeks. The intravenous administration of dextrose and physiologic saline solution is helpful because the patients are usually severely dehydrated.

In a recent more detailed article concerning the diagnosis and treatment of the emergencies associated with disease of the ductless glands, including the parathyroids, Kepler made this significant statement: "It is a curious and unfortunate fact that in the first four of these conditions, gastrointes-

tinal symptoms may be conspicuous and consequently may overshadow the less spectacular but more diagnostic symptoms which are indicative of the organ that is at fault "

COMPLICATIONS ARISING DURING TREATMENT OF OR FOLLOWING OPERATION ON THE DIGESTIVE TRACT

Extra renal Uremia (Alkalosis, Hypochloremia, Azotemia) We have already observed how hemorrhage, high intestinal obstruction, and disease of certain ductless glands may produce biochemical changes of sufficient degree to constitute a grave emergency. Dehydration, disturbance of the acid-base equilibrium of the blood, increased breakdown of endogenous proteins, oliguria, and probably temporary dysfunctions of the liver and kidneys seem to be the factors chiefly instrumental in bringing about this form of toxemia. The disturbance of water and inorganic salt balance is of primary importance, and clinical experience has repeatedly shown that it can be brought about by a wide variety of causes which may be both functional and organic in nature. Intractable vomiting of hysteria or psychoneurosis, acute alcoholism, acute gastroenteritis, hyperemesis gravidarum, the marked loss of gastric juice resulting from vomiting, from repeated gastric lavage, from continuous suction or from duodenal fistula, and the loss of body fluids as the result of a severe diarrhea, salt poor diets in renal and cardiac disease, hepatic disease, and induced severe diuresis may precipitate as severe a toxemia as that induced by high intestinal obstruction. The administration of alkalis to patients with peptic ulcer who for one reason or another are susceptible to the drug will bring about the same effect. Curiously enough, regardless of the wide diversity of causes, the morbid physiochemical changes in the organism are practically identical, namely, a rise in the concentration of urea and nonprotein nitrogen in the blood (uremia), a reduction in the plasma chlorides (hypochloremia), an increase in the carbon dioxide combining power of the plasma (alkalosis), and dehydration.

The diagnosis is based on the toxic manifestations and on the chemical examination of the blood. When patients are treated with alkalis the first symptoms are a distaste for milk, headache of variable severity, metallic after-taste, nausea, vomiting and vertigo, and frequent intensification of all these symptoms after the patient has taken an alkaline powder. As the intoxication progresses, irrespective of the original cause, whether functional or mechanical, one observes a flushed face, increasing nervous irritability, anxious expression and dehydration. In extreme cases there are incoherence, semiconsciousness and tetany. Delirium, coma and death may result if proper treatment is delayed.

Intestinal obstruction at a level lower than the jejunum also gives rise to azotemia and dehydration, but with a normal concentration of the plasma chloride and a variable acid-base equilibrium. This was observed by

Falconer and Lyall in 13 cases of obstruction of the small intestine and in six of obstruction of the large intestine. Acidosis of a nondiabetic and non-nephritic nature was observed in eight cases. In order to correct a seriously decompensated alkalosis and dehydration, for the past 15 years we have resorted to the intravenous administration of a 1 per cent solution of sodium chloride and 5 to 10 per cent solution of dextrose in 1000 c.c. of freshly distilled water, one to three times daily. The amount varies with the degree of toxemia, as indicated by the degree of chemical change in the blood. Ringer's solution in the amount of 80 to 100 c.c. per kilogram of body weight is a good substitute, especially if it is necessary to administer the fluid subcutaneously or intraperitoneally.

In the treatment of acidosis, which occasionally is encountered in cases of obstruction of the lower part of the small bowel and colon, in advanced stages of hepatic cirrhosis, in severe diarrhea, in fistulas of the small intestine and biliary ducts, 100 c.c. per kilogram of body weight of a mixture of isotonic sodium *r*-lactate, and isotonic or slightly hypotonic Ringer's solution in the proportion of 60:40 as recommended by Hartmann, has proved effective. Ringer's solution alone is useful. Kirk prefers an isotonic (1.3 per cent) solution of sodium bicarbonate. The dose of sodium bicarbonate necessary to restore the alkaline reserve to normal values can be calculated rather accurately by means of the nomogram of Palmer and Van Slyke. The daily urinary excretion should amount to 1500 c.c. to insure adequate renal function. Maddock and Collier recently have shown that a dehydrated patient requires at least 5000 c.c. of fluid daily. Where circumstances permit, as much fluid as possible should be given by mouth, the remainder should be given rectally or parenterally.

Hypoproteinemia and Gastric Retention In certain gastrointestinal disorders there may be an inadequate intake of protein or an inadequate absorption of ingested protein from the gastrointestinal tract with resulting reduction in the level of the serum proteins and of the colloid osmotic pressure which they exert. "War edema" and "prison dropsy" and the anasarca that frequently occurs in spile and certain diarrheas are examples of nutritional edema. It is a well-known fact that hypoproteinemia may occur in hepatic cirrhosis and that the low concentration of serum proteins often is intimately related to the formation of edema and ascites.

Hypoproteinemia can cause malfunction of a stoma following a Billroth I or Billroth II procedure, or after a gastrojejunostomy for obstructing duodenal ulcer. It thus may cause marked impairment of gastric emptying and subsequent toxemia. Recent observations by Jones and Eaton, Barden, Ravdin and Frazier, Mecray, Barden and Ravdin disclose the fact that hypoproteinemia and edema of the gastric mucosa must be considered as possible causes of such retention in cases in which a faulty surgical technic is highly improbable. According to Falconer and Lyall, this edema may be easily aggravated by the injudicious administration of saline solutions. They have estimated that 15 to 20 Gm. of sodium chloride daily are adequate to

correct chloride deficiency This may be given as 1500 to 2000 c c of 1 per cent solution of sodium chloride Any additional fluid required may be administered orally, rectally or parenterally in the form of a 5 per cent solution of dextrose These authors further observed that the intake of salt should be restricted to 10 Gm daily (1000 c c of 1 per cent solution) if the value for the plasma chloride approaches to 550 mg per 100 c c The diminution in osmotic pressure as the result of decreased concentration of plasma chlorides probably accounts for the tendency to edema which arises when the tissue reserves of chloride are raised Coller, Dick and Maddock have shown that edema is more the result of the administration of excessive amounts of sodium chloride than of large quantities of water A high protein diet and transfusions are important factors in raising the concentration of the serum proteins

SUMMARY

A wide variety of diseases and disorders frequently gives rise to disturbances predominantly of gastrointestinal nature and of sufficient severity to constitute an emergency Differentiation of an acute abdominal condition that requires prompt surgical interference and a nonsurgical one is the most important function of the physician

In chronic lesions of the digestive organs the more common complications, perforation, hemorrhage, and obstruction, frequently give rise to conditions which constitute an emergency Serious disorders engendered by disease remote to the abdominal organs, those of pulmonary, vascular andcretory systems in particular, are chiefly of a gastrointestinal nature and frequently overshadow the less spectacular but more diagnostic symptoms which are indicative of the organ that is at fault

Toxemia, variously designated as extrarenal uremia, hypochloremia, azotemia, alkalosis, or nondiabetic acidosis, is a frequent occurrence and constitutes an emergency incident to certain forms of treatment, preoperative states, or postoperative complications Of less frequency and gravity is hypoproteinemia, an important cause of edema and postoperative impairment of gastric motor function The successful management of these common gastrointestinal emergencies necessitates their timely recognition and the prompt institution of adequate therapeutic measures

REFERENCES

- 1 ABELL, IRVIN Acute abdominal catastrophies, Jr Am Med Assoc, 1937, cv, 1241-1245
- 2 BARDEN, R P, RAVDIN, I S, and FRAZIER, W D Hypoproteinemia as a factor in the retardation of gastric emptying after operations of the Billroth I or II types, Am Jr Roentgenol and Radium Therap, 1937, xxxviii, 196-202
- 3 BOTHE, F A, and BEARDWOOD, J T, JR The evaluation of abdominal symptoms in the diabetic, Ann Surg, 1937, cv, 516-520
- 4 CHRISTIANSEN, TAGF Biochemical changes in the organism produced by massive intraintestinal hemorrhage, Rev Gastro-Enterol, 1937, iv, 166-180

- 5 COLLIER, F A, DICK, V S, and MADDOCK, W G Maintenance of normal water exchange with intravenous fluids, Jr Am Med Assoc, 1936, cvii, 1522-1527
- 6 DIETRICH, K D Differential diagnosis between gastro-enteritis and appendicitis, Radiol Rev, 1937, iix, 203-209
- 7 FALCONER, M A, and LYALL, A The requirements of sodium chloride, Brit Med Jr, 1937, ii, 1116-1118
- 8 FALCONER, M A, and LYALL, A Blood chemistry in intestinal obstruction changes in response to treatment, Lancet, 1937, ii, 1472-1477
- 9 GRAHAM, R R The treatment of perforated duodenal ulcers, Surg, Gynec and Obst, 1937, lxiv, 235-238
- 10 GUERRY, LE G Quoted by Singer, H A
- 11 HARTMANN, A F The prevention and treatment of severe disturbances in water and electrolyte balance, Jr Iowa State Med Soc, 1937, lxxvii, 451-457
- 12 HILDEBRANDT, A Quoted by Singer, H A
- 13 JONES, C M, and EATON, F B Postoperative nutritional edema, Arch Surg, 1933, lxxvii, 159-177
- 14 KEPLER, E J Diagnosis and treatment of the emergencies associated with disease of some of the ductless glands, Med Clin North Am (In press)
- 15 KIRK, ESBEN Treatment of non-diabetic acidosis with intravenous injection of isotonic sodium bicarbonate solution, Acta med Scand (Suppl), 1936, lxxviii, 936-941
- 16 KLOSTERMEYER, W Die akute Gastritis unter den Erscheinungen einer Ulkus-Perforation, Munchen med Wchnschr, 1937, i, 695-697
- 17 MADDOCK, W G, and COLLIER, F A Water balance in surgery, Jr Am Med Assoc, 1937, cviii, 1-6
- 18 MCCRAY, P M, BARDEN, R P, and RAVDIN, I S Nutritional edema its effect on the gastric emptying time before and after gastric operations, Surgery, 1937, i, 53-64
- 19 MEULENGRACHT, E Treatment of haematemesis and melaena with food the mortality, Lancet, 1935, ii, 1220-1222
- 20 SINGER, H A Morphine as an aid in diagnosing acute abdominal affections, Am Jr Surg, 1936, lxxiv, 5-11
- 21 WILLIUS, F A Angina pectoris and surgical conditions of the abdomen, Ann Surg, 1924, lxxix, 524-532
- 22 WITTS, L J Haematemesis and melena, Brit Med Jr, 1937, i, 847-852
- 23 ZIEROLD, A A Quoted by Singer, H A

CLINICAL OBSERVATIONS, COMPLICATIONS, AND TREATMENT OF ACUTE UPPER RESPIRATORY TRACT INFECTIONS *

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NOTWITHSTANDING the fact that medical literature abounds with discussions concerning acute upper respiratory tract infections, one need not apologize for bringing the subject to the attention of this audience. Roughly speaking, these infections account for about 50 per cent of the time lost from work in this country (Brundage (1928¹)). Dochez² makes the statement that "epidemiological studies indicate that on the average every man, woman, and child in the United States experiences about two and one-half colds each year." While such a statement is not readily capable of proof, the fact remains that no other condition disables manpower to the extent accomplished by upper respiratory tract infections.

The present study is not concerned with epidemiology, nor with etiology, nor with pathways of infection. It deals with the care, in Stillman Infirmary of Harvard University, of 1667 cases of acute respiratory infection treated by myself and associates during the period, September 1935 to March 1, 1938. The subjects were undergraduates and graduate students at Harvard, the principal age range being from 17 to 25 years. The main purpose is to make a plea for simple treatment, the fruits of which are perhaps best indicated by the relatively small list of complications of all sorts occurring in this series.

The clinical picture in general may be characterized by the following: congestion of the nose and paranasal sinuses, mucoid or purulent nasal discharge, malaise, and often fever, cough and sore throat. We have included a few cases of simple coryza and we have made no diagnosis of influenza, since the evidence is not yet clear that the virus of influenza may act without producing the usual picture of prostration and depression characteristic of this infection. We have not been able to separate clearly the hypersensitive or allergic group among our patients, described by Spiesman and Arnold³. Fifty-seven cases were admitted on the day of onset following a chill, about 4 per cent of the total number. All of these had fever lasting one to three or four days, some of them showing normal physical examinations. Twenty-four per cent were admitted one day after onset, 30 per cent after two days, 17 per cent after three days, and 25 per cent after four or more days of illness. The patients in this series spent 7,708 days in the Infirmary. If we add to this the days of partial disability due to illness before admission to the Infirmary, information on which is not complete, the total of partial and complete disability is in excess of 25,000 days, a time span of

* Read at the New York meeting of the American College of Physicians, April 6, 1938.
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TABLE I
Upper Respiratory Tract Infections, Stillman Infirmary, Sept , 1935–March 1, 1938

Total Number	Total Infirmary Days	Duration in Infirmary					
		Days 1-6		Days 7-10		Days 11+	
		Total Number	Average Stay	Total Number	Average Stay	Total Number	Average Stay
1667	7708	1400	3 6	193	7 8	74	16 4

All admissions to Stillman Infirmary during same period = 4268
Respiratory infections = 39%

more than 70 years In our out-patient clinic for undergraduates, 2,632 respiratory infections were reported during the academic year, 1935–36, and 2,280 during 1936–37 Since the undergraduate group comprises about 3,700 men, there has been roughly one respiratory infection per year for 60–70 per cent of the total, considered serious enough to report Many of these were treated either at home or by rest in their rooms

In passing it is of interest that the curve of incidence of respiratory infections in this series, shown in chart 1, follows rather closely the curve published by J G Townsend ⁴

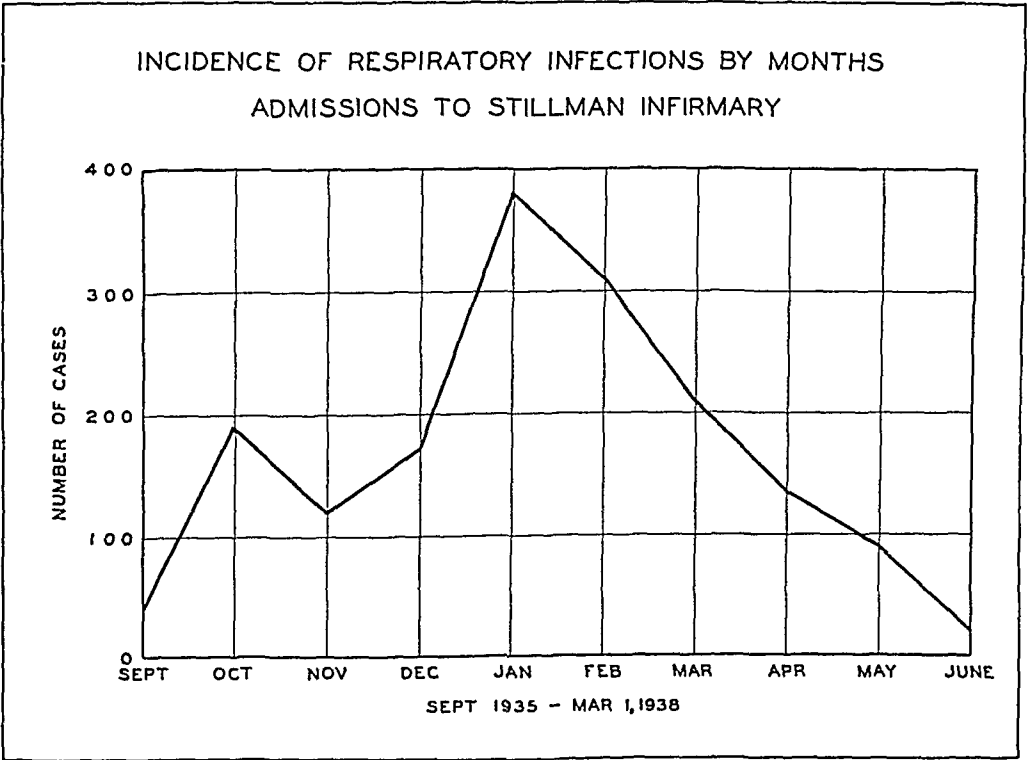


CHART I

Relatively minor variations occur from year to year in the clinical picture of the usual respiratory infections. The present series is composed for the most part of the more severe cases occurring during the period of observation. The notations included in table 2 cover only outstanding findings. Fever occurred in more than half the cases, chills in only 57 but chilly sensations were common. The complaint of aches and pains was not as frequent as is generally supposed in the syndrome usually called "grippe." Soreness of the throat was noted in 309 instances, although clinical evidence of pharyngitis was present in the majority of the cases. The diagnosis of laryngitis was restricted to the patients having partial or complete aphonia. The cases of acute tonsillitis presented the usual typical clinical picture of this infection. The diagnosis of bronchitis was not made unless the pulmonary râles characteristic of this state were present. Chronic cervical adenitis is not uncommon but the present findings are restricted to swollen tender glands presumably associated with the current infection. In certain

TABLE II
Clinical Observations

Fever One or More Days	Chills	Aches and Pains	Sore Throat	Laryngitis
881	57	109	309	83
Acute Follicular Tonsillitis	Bronchitis	Cervical Adenitis	Toxic Erythema or Rash	Palpable Spleen
28	22	195	26	28

cases, toxic erythema may closely simulate scarlet fever, but the latter diagnosis was excluded on other grounds. A few cases exhibiting a morbilliform rash required isolation because of resemblance to measles, but the rash was unaccompanied by mouth lesions and usually faded in two days or less. One case had petechial lesions beneath the clavicles and scattered elsewhere characteristic of those seen in sub-acute bacterial endocarditis.

The occurrence of a palpable spleen in 28 cases with or without accompanying adenitis in the presence of respiratory infection is new in our experience. These cases must be differentiated from cases of acute infectious mononucleosis. The blood picture for two or three days may show 20 to 25 per cent of mononuclear cells, with rapid return to a normal differential count. They probably represent cases frequently diagnosed as mononucleosis in which the heterophile reaction is negative.

White blood cell and differential counts were done in only 23 per cent of this series. The fact is mentioned here merely to point out that in the absence of known complications 35 per cent of these patients had white

counts ranging from 10,000 to 23,000 This is contrary to the usually accepted opinion that uncomplicated cases of so-called "grippe" have as a rule a leukopenic response

We wish to lay particular emphasis on the relatively small number of major complications encountered, listed in table 3 Many of the cases of otitis media had developed before the patients were admitted to the Infirmary The one case of mastoiditis did not require operation in the opinion of several consultants With reference to the surgical drainage of antra, it is our opinion that this procedure is not commonly necessary Irrespective of roentgen-ray findings showing complete clouding of one or both antra, many such cases will clear up in the course of two or three weeks with simple bed care It would be a rare case indeed in which surgical drainage of antra should be advised or attempted until well after all other signs of the acute infection have subsided Failure to observe a rule so simple may lead to serious trouble both present and in the future Observance of this rule will abolish much of the necessity for the use of prontosil in the treatment of acute sinusitis In this connection it is well to remember that the

TABLE III
Major Complications

Otitis Media		Mastoiditis	Antra Drained Surgically	Peri- tonsillar Abscess	Pneumonia
Secretory	Purulent				
20	9	1	2	1	52

complaint of chronic sinusitis is often an obsessive characteristic and that correction of existing maladjustments will produce more effective results than treatment directed at the local condition

Of the 52 cases of pneumonia, only four were due to type specific pneumococci One was due to hemolytic streptococcus The great majority of the cases we believe represent a virus pneumonia, with partial or complete involvement of one lobe of the lungs Spread of the process to another lobe occurred in some cases On admission to the Infirmary these cases could not be differentiated from the usual type of respiratory infection accompanied by fever As a rule the first evidence of the presence of a pneumonic process was obtained by roentgen-ray examination on the fourth or fifth day after admission Further observations on this subject will be considered in another communication One death occurred in a Boston Hospital in a case of Type I pneumococcus pneumonia, due to acute toxic nephrosis The administration of Type I serum may have accounted for the nephrosis

A matter of great interest is the fact that we have not encountered acute

involvement of joints in any case. If acute infectious arthritis occurs incident to upper respiratory infections, we believe it to be an uncommon sequela. During the period under consideration we have seen only two cases of acute rheumatic fever in the student body. No case of acute nephritis has developed. An attack of asthma was apparently precipitated in 10 cases, all having prior histories of asthma, hay fever complicated two cases, and diarrhea occurred in twenty.

Common-sense treatment of acute upper respiratory tract infections, including the common cold, with or without fever, requires bed care, a return to the principle established by Hippocrates. Time, trouble, and money will often be saved by the early institution of this method. Whatever the specific etiological factors may be, it appears clear to us that fatigue of body and mind in adult patients plays a rôle in the precipitation of these infections not generally recognized. The main principle of treatment should be rest. We believe that energetic local treatment produces irritation of the nasopharyngeal membranes, often prolonging the course. We do not advise the use of sprays, nose drops containing ephedrine, adrenalin packs in the nose, or painting the throat with argyrol or dyes. Through many recorded observations of the past, it has been known that the mucous membrane of the nasopharynx is especially sensitive to temperature changes and other stimuli. The present work of Drinker and his collaborators⁵ is opening a new vista concerning the absorptive properties of this area. The mechanism is so complex that we do not yet know enough to assist it intelligently when the usual infections are present. That irritation is set up by the free use of ephedrine, for example, is no secret and the after-effects of surgery in the nose, of whatever kind, suggest that damage may follow that is not readily repaired. Surgery in this area at all times should be approached with caution. Our results in the present series of cases indicate that few complications result from the simple policy of instituting bed care. Salicylates and codeine are used for comfort. Laxatives are not usually prescribed. There is reason to believe on the evidence of Kerr⁶ and others, that control of temperature, humidity, and dust would add greatly to the effectiveness of treatment.

That prevention of upper respiratory infections by vaccines has little to support it, has been well shown^{7, 8, 9, 10}. Lacking specific means of therapy, the greatest advance on the problem at the moment would be made if we could teach ourselves and our patients how to live within our physical resources, and especially within those of our central nervous systems. Such influences as chilling of the body, weather changes, irritative substances in the atmosphere, and contagion, must be taken into account, but granting these, under ordinary circumstances, the rôle played by the tension of living must be recognized more generally in our assault on the problem.

My appreciation is acknowledged of the generous time given by associates in the Department of Hygiene in reviewing the case histories.

REFERENCES

- 1 BRUNDAGL, D K Importance of respiratory infections as a cause of disability among industrial workers, Pub Health Rep, 1928, xliii, 603
- 2 DOCHEZ, A R A limited consideration of certain aspects of acute infection of the respiratory tract, Medicine, 1933, xii, 245
- 3 SPIESMAN, IRWIN, and ARNOID, LLOYD Host susceptibility to common colds, Am Jr Digest Dis and Nutr, 1937, iv, 438
- 4 TOWNSEND, J G Epidemiological study of the minor respiratory diseases, Pub Health Rep, 1924, xxxiv, 2669
- 5 DRINKER, C K Personal communication
- 6 KERR, W J The common cold, Jr Am Med Assoc, 1936, cxvii, 323
- 7 SHOILY, A I VON, and PARK, W H VII Report on the prophylactic vaccination of 1536 persons against acute respiratory diseases, Jr Immunol, 1921, vi, 103
- 8 FERGUSON, F R, DAVIG, A F C, and TOPLEY, W W C The value of mixed vaccines in the prevention of the common cold Jr Hyg, 1927, xxvi, 98
- 9 BROWN, W E Vaccine in the prevention of the common cold, Am Jr Hyg, 1932, xv, 36
- 10 KNEELAND, YALE, JR The protection afforded by vaccination against secondary invaders during colds in infancy, Jr Exper Med, 1934, l, 655

CONSTITUTIONAL FACTORS IN ARTHRITIS WITH SPECIAL REFERENCE TO INCIDENCE AND RÔLE OF ALLERGIC DISEASES

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CHRONIC arthritis of the atrophic and hypertrophic types is the most common chronic illness and ranks first among the causes of disability. The high incidence of this disease is indicated by a survey in Massachusetts where 32 per cent of the total population and 30 per cent of the disabled were found to be suffering from rheumatoid disease¹. In spite of its prevalence the medical profession as a whole is discouraged or at least apathetic in its treatment.

There is no agreement among students of chronic arthritis as to the basic factors or diathesis predisposing the patient to the disease nor is there agreement as to the nature of the causative agent. The American Committee for the Control of Rheumatism stated that it "conceives of the disease as a generalized disease with joint manifestations". Yet the joint manifestations must be present to diagnose the disease.

This confusion led me to analyze my first 50 cases in which arthritis was the chief or a prominent complaint, not only from the standpoint of the signs and symptoms of arthritis but also from the standpoint of complications disclosed both in the history and physical examination. Certain relationships appeared quite striking. In the next 50 cases special attention was paid to them. An analysis of this series again suggested further studies. As a result the statistics which follow will be in part based on 150 consecutive cases, while some of the statistics will be based on separate series of 50 patients. At times this may be confusing but it is difficult to get the same data in a series of patients unless special thought is given to it.

In this paper both clinical types of arthritis, the atrophic and hypertrophic have been grouped together as it appears that fundamentally they are the same disease. However as this is not proved and time does not permit a defense of this position the series was classified as to predominant type.

Type	Number of Cases	Per Cent
Hypertrophic	95	62 $\frac{1}{3}$
Atrophic	47	31 $\frac{1}{3}$
Mixed	8	5 $\frac{1}{3}$

There were 22 males or 14 per cent and 128 females or 86 per cent. This series is rather overloaded with females as it is generally considered that the incidence is only about twice as great among females. The average age of the 150 patients was 53.3 years.

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CLINICAL MANIFESTATIONS OF ARTHRITIS

My studies lend support to the conception that arthritis is a generalized disease with joint manifestations. In the first place the symptoms as given by the patient are not confined to the joints, secondly, the general symptoms tend to precede joint symptoms or to persist during periods of freedom from joint symptoms, and finally there are definite constitutional trends shown by the group.

The first 50 cases were tabulated with regard to the major symptoms shown

Class of Symptoms	Symptoms	Per Cent
Constitutional	Mild malaise or feeling of being less well	84%
	Of inability to sleep well not necessarily from pain	74%
	Nervousness and depression	74%
Gastrointestinal	All varieties as will be taken up later	
	Of various grades of constipation	88%
	With two or more stools a day	8%
Circulatory	Facial pallor and delayed capillary circulation in the finger tips in all active cases	
	Numbness of extremities	54%
	Cramping of muscles	32%
Skeletal	Pain	100%
	Stiffness	74%
	Swelling of joints	50%
	Weakness or atrophy of muscles	34%

It will be noted that only 50 per cent were recorded as having joint swelling. Arthritis in the spine, sacroiliac and hips will not give joint swelling perceptible on ordinary examination nor will an early joint involvement without effusion and before marked thickening of the capsule.

A study of the clinical course of arthritis as shown in the histories again illustrates the generalized character of the disease. Usually there is a history of 'never being sick but never being really well,' of constipation and of poor circulation for years before the onset of joint symptoms. We have all seen cases with well marked hypertrophic spurs who have never or have only recently had joint symptoms, an experience which forces us to the conclusion that arthritis has been present without joint symptoms. Consequently the disappearance of joint symptoms cannot be regarded as proof of the cure of the disease. The last 50 patients in the series were studied with this in mind. In 48 patients the age of onset of the first joint symptoms was noted and in 49 the age of onset of continuous joint symptoms. In 12 of 23 cases of the atrophic type and in 9 of 27 cases of the hypertrophic type the onset of the first joint symptoms and that of continuous joint symptoms were the same. Consequently 58 per cent of the cases had definite attacks of joint symptoms with periods of freedom before the onset

of continuous joint symptoms The fact that 20 per cent of the cases were under 45 and 10 per cent had symptoms less than one year makes it probable that even a greater per cent would have remissions if followed long enough

CONSTITUTIONAL BACKGROUND

Certain hereditary and constitutional factors seem to furnish the soil on which arthritis develops In 73 per cent of 150 cases there was a family history of allergic diseases and in 52 per cent a history of arthritis In 80 per cent one or the other or both were noted Due to the lack of specific knowledge about blood relatives these figures from the histories are more suggestive than absolute

In the first 50 cases a definite trend to longevity was noted, so that in the subsequent 100 cases the ages of 196 of the 200 parents were obtained One hundred five of these had died at ages over 70 or were still living at an age greater than 70 Fifteen parents under 70 were still alive Taking their ages and using the American Men's Ultimate Mortality Table it was computed that 9 of the 15 living should reach 70 Thus 114 or 57 per cent of the parents of these arthritics live to 70 Assuming that the average age of the parents at the time of birth of the patient was 30 and using the American Experience Mortality Table for comparison we find that 45.1 per cent of people aged 30 would reach 70 and 57 per cent would reach a fraction over 65 Since longevity has been proved to be inherited arthritis may be said to have a constitutional background of longevity

The group showed a definite tendency to low blood pressure at the initial examination, but as the group as a whole was not studied carefully and repeatedly from this point of view statistics would be misleading However, only 4 or 2.7 per cent of the 150 patients had diastolic pressures of 100 or over Only 2 per cent of the last 100 showed persistent albuminuria and casts and low specific gravity indicative of any considerable grade of nephritis An analysis of the blood pressures and urinary findings indicates that arthritics develop primarily arteriosclerosis rather than hypertension and nephritis

FOCAL INFECTION

Having found that there is a constitutional background and generalized physiological disturbances associated with the joint symptoms of arthritis we turn to the subject of focal infection Pemberton² noted in one series of 545 cases of arthritis demonstrable foci in 70 per cent while in another series of 100 non-arthritics 87 per cent had demonstrable foci of infection In this second series in a general medical ward, nephritis and cardiac conditions were the chief disease states Thus focal infection is not a condition peculiar to arthritis In reviewing 100 cases in which special attention was given to the history of removal of foci I found I was entering upon a well tilled field as most of the patients had had previous medical care and

87 per cent had had active disease more than one year. The figures illustrate the persistence of arthritis in spite of the absence of foci in the usual location, teeth, tonsils, sinuses, gall-bladder and appendix.

In regard to teeth 25 per cent of the patients were edentulous, 13 per cent having been so before the onset of their arthritis, 12 per cent having had all the remaining teeth extracted because of it. In another 28 per cent some teeth had been extracted because of rheumatism. A further 8 per cent were found to require dental care. The tonsils were well attended to; in 28 per cent they had been removed before the onset of the arthritis and in 27 per cent tonsillectomies had been performed for the joint symptoms. Thus in 55 per cent rheumatism persisted in the absence of tonsils. The appendix had been removed in 23 per cent and probably in 2 others who had had pelvic operations. Only 8 per cent had had nasal operations, which is noteworthy as a large number had nasal symptoms as will be shown later. Six had had gall-bladder operations. In two others there was a history of jaundice in adult life but none of colic. Many of the patients had had gall-bladder roentgen-ray studies at some time during their illness. As to genito-urinary foci one had pus in the prostatic secretion and five gave a history of urinary tract infections in the past.

These figures are given not with the intent of proving that removal of foci is of no value in arthritis but to emphasize that arthritis will persist after the usual foci have been removed. Many physicians have observed that marked benefit from the removal of foci in arthritis is rarely seen except early in the course of the disease, and these patients in my series represent the ones who were not permanently benefited by such removals.

It would be poor medicine, however, to tell a person who had an abscessed tooth that he should neglect it because careful examination brought out no evidence of any systemic pathological disturbance from it. Whether a focus of infection is the direct cause of joint symptoms or not, it may when added to other factors already operating be sufficient to upset the physiological balance of the patient and precipitate symptoms just as other infections, fatigue, meteorological disturbances and menstruation will. Many of my patients gave a history of being benefited by removal of foci, many were made worse and most noticed no effect. Focal infection in arthritis presents no more urgent problem than in other diseases and should be attacked with due regard to the patient's vitality.

FREQUENCY OF ALLERGIC MANIFESTATIONS

When the first 50 cases were reviewed, the incidence of a history of asthma, hay fever, hives, eczema, bilious headaches and canker sores was very high. The incidence of asthma was 4 per cent, that of nasal allergy 20 per cent, hives 12 per cent, eczema 16 per cent, migraine 14 per cent and other sick headaches another 26 per cent, canker sores 36 per cent. It was found that 78 per cent had at least one of these allergic manifestations.

Eczema, hives, canker sores and sick headaches are generally regarded as being due to protein sensitization in which food is the offending factor, while asthma and nasal allergy may or may not be. Curiously enough I had found four of the eleven patients in whom no note was made of other evidence of allergy, sensitive to foods in the diet I was using. As was mentioned earlier 96 per cent of this first group of 50 had abnormal bowel function. The next 100 cases were studied carefully from the standpoint of food allergy.

The following table shows the frequency and distribution of the various types of allergic manifestations in the next 100 cases as noted either in the past history or the progress notes.

Nasal allergy	50
Asthma	11
Eczema	13
Bilious headache including migraine	38
Canker sores	42
Gastrointestinal	94
Bladder	17
Urticaria	13

DISTRIBUTION AMONG PATIENTS

DISTRIBUTION AMONG PATIENTS

	6 Types	5 Types	4 Types	3 Types	2 Types	1 Type	None
No Pts	1	6	23	29	28	10	3

In two of the three cases where no allergic manifestations were noted the history was inadequate and treatment too short to determine the presence of allergic manifestations and in one case the symptoms might have been caused by an active tuberculosis, observation again being too short to be certain.

It is noteworthy that 94 of the 100 patients had gastrointestinal symptoms that were considered due to food allergy. In 6 of 8 cases where the period of observation was less than one month, a history of food disagreement was considered adequate evidence. In 88 of the remaining 92 cases of the series the presence of food allergy was proved by the precipitation of their gastrointestinal symptoms by the addition of offending foods, and the relief of the symptoms by the subsequent removal of the foods. This statement that 94 per cent of this series of arthritics had symptoms of gastrointestinal food allergy does not mean that food allergy is the only disturbance present in the gastrointestinal tract and in fact it appears at times to be conditioned by other abdominal pathologic processes.

GASTROINTESTINAL TRACT IN ARTHRITIS

At this point it would be well to review briefly the gastrointestinal symptoms present in this series. A study of the last 50 patients from the standpoint of their gastrointestinal symptoms failed to reveal any characteristic syndrome, such as is found in peptic ulcer. Perhaps the most characteristic notation was the patient's observation of gastrointestinal disturbances following ingestion of certain foods or overeating. The table below shows the incidence of the more common gastrointestinal symptoms, the first column shows the percentage in which the symptom was mild or inconstant, the second in which it was severe or of concern to the patient and the third the total per cent in which the symptom was found. Twenty per cent of the

Symptom	% Mild	% Severe	% Total
Anorexia	40	10	50
Coated tongue	42	20	62
Nausea and vomiting	32	12	44
Distress after eating	26	20	46
Belching	22	18	40
Heart burn	28	4	32
Bloating	36	18	54
Soreness and cramping	32	8	40
Flatulence	16	14	30
Constipation			86
Occasional laxative	22		
1-5 a week		20	
Daily		44	
Excessive number stools	16	8	24
Mucus in stool	32	14	46
Periodic bloody mucus	6		6

group did not complain of any severe gastrointestinal symptoms. Of the 14 per cent without constipation 10 per cent gave a history of mucus in the stools including in 8 per cent an excessive number of stools. The remaining 4 per cent complained of no symptoms referable to the gastrointestinal tract except a coated tongue. Both of these later showed disturbances due to food sensitization.

These figures indicate that arthritics as a group have gastrointestinal symptoms but of no definite pattern, their severity correlates more with the nervous instability of the patient than with the severity of the disease. Three of these patients had definite pathologic lesions, one gall stones, one an abdominal fistula with three openings into the bowel and one had had repeated attacks of diverticulitis.

My experience with gastrointestinal roentgen-ray studies has been very limited. Consequently I will quote directly from Pemberton's³ book, "Arthritis and Rheumatoid Conditions, Their Nature and Treatment."

The type of colon which is met with in many arthritics is characterized chiefly by a tendency to greater caliber, greater length, a more convoluted appearance and sometimes reduplication. It is to be borne in mind that many apparently healthy

people harbor diseased tonsils for example, and by the same token the bowel may be potentially the cause of disease, by virtue of faulty anatomy or dysfunction, without having as yet brought this about. The colon will, therefore be found in a certain limited proportion of apparently normal subjects also to approximate the type here described. Other departures from theoretical normality show themselves in the gastrointestinal tract as the result of roentgen-ray studies among arthritics. These are chiefly in the direction of a somewhat delayed transit of the barium meal together with more or less ptosis of the stomach and colon. It is of the highest importance to note that marked stasis may exist in the presence of apparently adequate daily bowel movements. Another outstanding feature which is encountered in a given proportion of cases is the regurgitation of the barium through the ileocecal valve.

The "marked stasis" of which Pemberton speaks can frequently be shown by giving carmine dye by mouth. This method is used in metabolic work to mark the beginning and end of the portion of the stool belonging to a certain period of the experiment. In a strictly normal bowel action definite segments of stool show the dye. In some arthritics the dye may appear in from 24 to 72 hours and continue up to 120 hours. It is uncommon to find one segment of the stool colored and the other not colored.

DISCUSSION

An attempt has been made to show the constitutional trends and the physiological disturbances that those who suffer from chronic joint disease of the so-called hypertrophic and atrophic varieties have in common. This was done to emphasize what has been observed already that an individual arthritic suffers from ill health as well as joint pain and that his ill health is not peculiar to him as an individual but that both the ill health and joint changes are part of the same physiological disturbance. Considerable space was given to allergic manifestations. Unfortunately attaching a name to a clinically common and unimportant phenomenon tends to exaggerate its importance in our minds, and this is especially true when the same name may be used for very serious conditions. An occasional crop of hives is just as much an allergic phenomenon as a severe urticaria but not by any means of the same clinical importance though it does indicate the same constitutional trend. Not every person but a large number do show allergic manifestations. Vaughan and Pipes⁴ made a survey of 500 persons and found 10.6 were frank major allergics and 49.8 per cent more were minor allergics with mild allergic symptoms in their past history. In the same journal Bret Ratner⁵ states that 7 to 10 per cent of the population are afflicted with allergy. Rowe⁶ found 35 per cent with allergic history or manifestations in a survey he made.

As to the mechanism of allergic reactions only the barest outline is warranted here. There appear to be two major factors. First a deficient or altered constitution on the part of the host which seems to be a derangement of intracellular digestion and second certain specific chemical and

possibly physical stimuli which will precipitate reactions in an individual because of changes brought about by the constitutional deficiency. An allergic individual is in his apparently normal physiological balance as long as contact with the antigenic substances is avoided as for example the freedom of a pure pollen hay fever sufferer at other seasons of the year.

Arthritis is coming to be looked upon more and more as an allergic phenomenon in the skeletal structure as is shown by the tremendous amount of tissue reaction in which only few or no infectious organisms can be demonstrated. Joint reaction to the streptococcus in rheumatic fever is an example of reaction to an infectious agent. The joint manifestations of scarlet fever, typhoid fever and undulant fever are other examples. Non-infectious agents causing joint symptoms may be illustrated by the joint symptoms in serum sickness. Cases are reported where foods cause effusion in joints. In chronic arthritis the agent must be active over a long period of time. Roentgen-ray changes in the bones are often not found when the first symptoms develop and their degree and type depend on the severity and duration of the reaction.

Many authors have looked upon the bowel as the chief focus of infection in arthritis. The contents of the bowel, both food and bacterial and also their breakdown products, offer an unlimited and more or less constant source of antigens for allergic reactions in joints. Normally the mucous membrane of the bowel offers a sufficient barrier to the noxious elements in the intestinal tract so that foreign proteins do not enter the blood stream in amounts in excess of the ability of the body to destroy them. Since arthritics in general show other manifestations of allergy an arthritic probably has a deficient parenteral digestion, but we must also consider whether factors are present in the bowel itself which allow an excess of foreign substances to pass through its mucous membrane to overtax an already deficient though otherwise adequate parenteral digestion. Evidence has been presented of a very high incidence of disturbance of the gastrointestinal tract in arthritis usually with stasis and accompanied by gastrointestinal food allergy.

Rowe⁷ in his book "Food Allergy" (1931) discussed the relation of food to arthritis. He mentions that Talbot (1917) and Cooke (1918) suggested food as a source of arthritic pain in certain patients and that Turnbull in 1924 noted relief of arthritic symptoms on diets based on skin tests. Rowe himself reported three cases. In his discussion he favored the view that arthritis was due to bacterial allergy but felt that in some cases it might be due to foods. More recently, in 1936, W. T. Wootton⁸ suggested that arthritis is an allergic reaction in joints to food or bacterial protein and that elimination diets should be used but states that allergic food reactions are rarer as age advances. G. T. Brown,⁹ in 1934, suggested that the factor of food sensitization should be considered in arthritis but that bacterial allergy was more important. Thus the association of food allergy and arthritis is being recognized.

RÔLE OF GASTROINTESTINAL FOOD ALLERGY

My studies on the 150 cases in this series suggest an explanation of the rôle of food allergy. A survey of the first 50 cases showed that no case that was freed from gastrointestinal symptoms and that regained apparently normal bowel function failed to gain relief from arthritis, and the converse—that those whose gastrointestinal symptoms failed to respond or became worse failed to make much improvement, or progress. Among those who improved were the ones in whom I had recognized food allergy and had eliminated the offending foods from their diet. This observation led me to investigate the problem of food allergy in the succeeding cases.

In working out an elimination diet in an uncomplicated case of arthritis the symptoms due to food allergy will usually clear up in from five to seven days both in the bowel and elsewhere, for example, in the nose, skin, lungs, etc. There is a marked improvement in the constitutional symptoms but usually not much change in the joint symptoms for another five to seven days, but then the muscle soreness and acute inflammation in the joints begin to subside leaving chiefly pain on motion, stiffness from adhesions and weakness due to muscle atrophy. Thus there is a two week cycle. Five to seven days for the bowel to become free from symptoms and five to seven more days for the acute joint reactions to subside. The subsequent introduction of an offending food in the diet is followed in from one to seven days by a return of the allergic symptoms and a few days later after the disturbance in the gastrointestinal tract is established, the joint symptoms increase. This will occur even after the ingestion of the offending food has ceased but before the gastrointestinal symptoms have subsided. Again about five days after the bowel symptoms disappear the rheumatic pain subsides. The observation that exacerbations of the rheumatic symptoms do not occur simultaneously with the development of allergic reactions to foods in other tissues of the body but tend not to appear until a well marked gastrointestinal disturbance is set up and that remissions in the rheumatic symptoms do not occur until after the gastrointestinal symptoms subside, suggest that the rheumatic symptoms are produced by antigens whose access to the joints are conditioned by the allergic reactions elsewhere, presumably the bowel.

An allergic reaction in the bowel is accompanied by disturbed motility and by edema of the mucous membrane. The increased permeability produced by the allergic reactions is suggested by a clinical observation. An individual with a bowel allergy, on a diet that agrees with him, can eat beets without the color appearing in the urine in appreciable amounts. The same individual when having an acute bowel reaction frequently will notice a pink tinge to his urine (on several occasions red enough to engender a phone call to the doctor). This observation suggests that the permeability of the bowel has been altered so that the beet pigment is allowed to pass

into the blood stream or else passes through more rapidly or possibly its digestion in the body is impaired

Bowel allergy is known to cause constipation and stasis. Constipation and stasis are present in a large proportion of arthritics. That it produces an increased permeability of the bowel is suggested by the beet pigment observation. Thus food allergy may produce both the colonic stasis and increased permeability of the bowel which would make the colon a likely focus for infection.

CONCLUSION

If arthritis is an allergic reaction in joints to foreign protein, living or dead, brought to it from the blood stream, then any portal of entry may theoretically be a focus. It is intended in this paper to imply only that the bowel is the most common focus. Tolerance to an antigen is only relative and probably depends on the efficiency of the mechanism of intracellular digestion. A coexisting food allergy may depress the tolerance to other antigens and it is well known that infection, focal or otherwise, weather, fatigue or menstruation are prone to lower the tolerance of an allergic individual. Again it is not meant to say that food allergy is the only disturbance in the bowel or always the prime one. I have seen one case of pure food allergy, which was freed from symptoms on an elimination diet, return to a regular diet without symptoms after a Jackson's membrane distorting the cecum was severed. Rae Smith in a personal communication to the author stated that adhesions were an important factor in one case in eight of the severe rheumatoid type of arthritis. Dietary deficiencies may play a rôle in the lowering of the resistance of the bowel mucous membrane. My thesis is that food allergy is the most common and in many cases the most important factor in the bowel disturbance that predisposes to chronic arthritis.

SUMMARY

In summary, arthritis is a pathological condition of the joints behind which there is a constitutional background and a widespread disturbance of the general physiology. There is an hereditary tendency to allergy, arthritis, longevity and a hereditary resistance to essential hypertension, and glomerular nephritis. It is a condition where progress may be aggravated by foci of infection in the teeth, tonsils, sinuses, gall-bladder, etc but where progress may persist in the absence of such foci. The type of reaction in the joint suggests an allergic reaction. This is made more probable by the almost universal presence of manifestations of specific sensitization in other tissues. The presence of disturbances in the bowel due to specific sensitization to food was shown in over 90 per cent of our cases. The clinical course of exacerbations under treatment suggests that these reactions in the bowel make it more permeable and cause the body to be

flooded with an excessive amount of antigens from the bowel to which the joint structures are sensitized

REFERENCES

- 1 BIGELOW, G H, and LOMBARD, H L Cancer and other chronic diseases in Massachusetts, 1933, Houghton, Mifflin Co, Boston
- 2 PEMBERTON, R Arthritis and rheumatoid conditions, their nature and treatment, 1935, Lea and Febiger, Philadelphia, pg 48-49
- 3 *Ibid*, pages 234, 235, 236
- 4 VAUGHAN, W T, and PIPES, D M Is there a correlation between food dislikes and food allergy? *Jr Allergy*, 1937, viii, 257-260
- 5 RATNER, B Does heredity play a role in the pathogenesis of allergy? *Jr Allergy*, 1937, viii, 273
- 6 ROWE, A H Food allergy, 1931, Lea and Febiger, Philadelphia, pg 19
- 7 *Ibid*, page 271
- 8 WOOTTON, W T, JR The role of allergy in arthritis, *Jr Arkansas Med Soc*, 1936, xxxii, 119-122
- 9 BROWN, G T Allergic phases of arthritis, *Jr Lab and Clin Med*, 1934-35, xx, 247-249

AFFECTIVE DISORDERS IN MEDICAL PRACTICE

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By affective disorders we mean those characterized by pathological changes in mood and disturbances of the emotions. There may also be many physical symptoms and complaints. Victims of the outspoken psychoses in this group make up 10 to 15 per cent of the patients in psychiatric hospitals. The practicing physician sees these patients relatively early and when we broaden our conception of affective disorders to include those occurring in more or less natural reaction to distressing situations and to physical illnesses we should the more readily realize their importance in medical practice.

Among the commoner affective disorders are the manic depressive psychoses, reactive depressions, and tension depressions, easily recognized as emotional disturbances when the affect is obvious but how often even then misunderstood and maltreated. Mr. John Doe's wife, Mary, aged 40, has been for two months sinking deeper and deeper into a depression. She is taken to an old friend of the family, a surgeon, let us say, who after hearing the story decides to give her a good talking to. "My dear Mary," he says, "I have known you for twenty years and in all that time I have regarded you as a faithful wife, a devoted mother, and a wonderful housekeeper. You have always been looked upon by your neighbors and friends as a model in these particulars. I cannot understand what has come over you. You are making your husband's life miserable by adding greatly to his cares and worries, you have lost all interest in your household duties, and you are neglecting your children at this crucial stage in their development. Please understand that this sort of thing must stop at once." At the conclusion of the lecture the poor, miserable creature who entered the office convinced that her own life was wrecked, leaves it with the forcible suggestion that she has also ruined the lives of her husband and children and this may thereafter be a central idea in her depression. Another friendly physician may be less severe or even sympathetic but nevertheless ends his consultation with the urgent advice that she 'snap out of it,' a milder suggestion that she is responsible for the whole sad affair, a confirmation to her of the feelings of self-blame of which she was already only too conscious. Most of us of course would not take such an attitude but would sympathize briefly with the patient, encourage her to look forward to recovery, arrange a plan of living giving particular thought to protection of the patient, to appropriate occupation, with a form of psychotherapy suitable to the mental status at the time.

But there are patients in whom the diagnosis is much more difficult

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and who are therefore often classed among the psychoneuroses. Among these may be some of the patients with tension depressions, or with merely the physical equivalents of a depression, headache, dizziness, palpitation, epigastric distress, constipation, exhaustion, insomnia. They may complain entirely of somatic distress and the variability of mood, loss of interests, poor concentration, inattention, indecision, self-blame, feelings of tension, panicky feelings, and suicidal ideas are found only by searching for them. Some of these patients are lost early by suicide because they are not recognized and protected. In the milder cases the physician may give the patient a measure of comfort along with careful guidance even though he may doubt his ability to shorten the duration of the illness, for usually these maladies are circumscribed with a definite onset and a definite offset, the time of which may not be predicted with any certainty.

There are psychiatrists who believe that the neuroses are primarily affective disorders, emphasizing the affect rather than the organ involved, and preferring to speak of "a neurosis with cardiac symptoms" rather than "a cardiac neurosis." These psychiatrists further believe that affective disorders can lead to organic changes. They may still further say that in many organic diseases the affect is of great importance for the symptomatology, for prognosis and for therapy.

Most of us internists have been trained from our medical infancy to think in terms of somatic pathology. Clinical observations of organic diseases and experimental procedures based on them are often capable of justification by proof. The results of psychic manifestations are very difficult of proof. Through the work of many physiologists, however (Beaumont, Cannon, Pavlov), we know and accept the demonstration that through the vegetative apparatus (the autonomic nervous system and the endocrine system) emotions can produce bodily changes in function including chemical changes in the blood. We are more or less familiar with the idea of the internal environment of the body or homeostasis as outlined by Cannon in contradistinction to the external environment so important in the social aspects of medicine. How much do we utilize these ideas that we have heard and accepted, or are they pigeonholed as merely academic ideas as far as our general concepts of disease are concerned? The whole question of emotions and bodily changes, or psycho-somatic inter-relationships, is of great interest to many physicians and I believe of great importance to all of us. The literature on this subject from 1910 to 1933 has been admirably digested and summarized in a monograph by H. Flanders Dunbar. The literature includes that of general biology, embryology, comparative anatomy, neuro-anatomy, physiology, psychology, psychoanalysis, and clinical work by surgeons, by physicians, and most of all by psychiatrists. It is interesting to note that the biologists in their philosophy approach so nearly the philosophy of the physicists. For example, McKimney is quoted to the effect that "emotion is the modification of energy (difference of potential) of the body by which the power in action of the body is aided or restrained,

increased or diminished, and that this difference of potential may be expressed both psychically and physiologically and that energy so expressed is the same in kind, though differing in organization, from that found elsewhere in the universe" This is not so different from the pronouncement recently attributed to Einstein

It is pointed out that the review of literature reveals three distinctly different attitudes among practitioners toward the relationship of psyche and soma in acute and chronic disease There is the organicistic bias, the psychic bias (equally fallacious), and the organismal point of view of psycho-somatic unity This third point of view has been preached for many years by the Meyer school of psychiatrists, by the psychoanalysts, and by Barker among the internists Meyer says, "What is of importance to us is the activity and behavior of the total organism or individual as opposed to the activity of single detachable organs" F Mohr is thus quoted, "There is no such thing as a purely psychic illness or a purely physical one, but only a living event taking place in a living organism which is itself alive only by virtue of the fact that in it the psychic and somatic are united in a unity" Bleuler thinks that the question, "physical or psychic?" is in many cases wrongly put and should be replaced by the question, "To what extent physical and to what extent psychic?"

The review relates to the possible importance of psyche in all the physical domains and from the standpoint of both clinical observation and experiment Only a few examples must suffice as illustrations

Under the general heading of Musculature, "Rheumatic Diseases" are considered Mohr wrote in 1925, "Observations made during the War provided ample evidence of the extent to which the so-called rheumatic diseases are increased or 'fixated' by psychic factors Of 100 cases that I carefully examined, 90, in which the illness had been of considerable duration, were cured by purely psychic treatment Here as probably in cases of sciatica we must recognize the vicious circle Pain, initially somatically conditioned, results in abnormal posture and muscle spasm, these are wrongly evaluated psychically, leading to increase of pains and again to abnormal posture, etc" J Levy notes that muscular or articular rheumatism is one of the most frequent diagnoses to be met in the practice of socialized medicine, in countries with social insurance the percentage of these cases outnumbers the percentage of tuberculosis cases He says that rheumatism has been proved to exist as a functional disease without primary organic alteration or, as we say today, as a neurosis of the motor organs He points to the eminently practical value of such a conception and to the necessity of psychotherapy Obviously here the term 'rheumatism' is used in a very broad sense and probably includes some of those cases often spoken of as muscular rheumatism, myositis, or fibrositis

In introducing the chapter on "Endocrines" Dunbar states, "The endocrines, it has been said, translate the tempo of the nervous system into the tempo of metabolism and vice versa They are therefore important

factors in the maintenance of equilibrium of organism in environment, and it is thus inevitable that those interested in the question of psychosomatic inter-relationships should find this field particularly inviting." In regard to the thyroid the syndrome of hyperthyroidism has been called the prototype of a nervous polyglandular disorder. The relationships of the glandular disorder and of the sympathetic nervous system naturally are stressed. The more extreme view of this disease would be as follows. The cause is an emotional disturbance that in a person with a peculiar constitutional predisposition operates through the thyroid gland and through the vegetative system in general to produce disturbances in many of the organ systems. There is produced, for example, in the heart, tachycardia, auricular fibrillation, cardiac dilatation, and cardiac failure. In the gastrointestinal system various functional disturbances, in the field of metabolism a marked increase in general metabolism, an elevation of the basal metabolic rate, loss of weight, emaciation, and perhaps a rarefaction of bones. The standard methods of treatment are not causal but symptomatic. The thyroid gland is treated by iodine medication and by sub-total thyroidectomy, thus interrupting the mechanism of the disease. For causal therapy the emotional disturbance must be discovered and treated. This may be superficial and easily disclosed, or it may lie at a deeper and less accessible level of the psyche.

In the chapter on the respiratory system the reviewer states that inasmuch as bronchial asthma is a controversial subject of considerable interest, the literature, as it pertains to the psycho-somatic problem, is reviewed in some detail. It is recognized that the modern literature concerning asthma is dominated by the concept of asthma as an allergic disease. Opinions as to the relative importance of psychic phenomena vary widely. Hansen writes, "In going over the English discussion of this subject (or the German, which is equally prone to extreme conclusions) one finds that points of view which apparently represent opposite poles can be maintained tenaciously only because neither side has sufficient experience to evaluate critically the arguments adduced by the other." There are numerous reports of successful psychotherapy, for example, Moos, a German internist, reports that in addition to milder cases he treated by intensive psychotherapy 16 asthmatics who were unable to work because of their disease. In all these cases the bronchitic lung signs disappeared at the end of the treatment. The emphysema subsided entirely or considerably except in two patients more than 50 years old. All cases ceased to have sputum and the Charcot-Leyden crystals and Curschmann's spirals disappeared also. The eosinophile cells in the sputum disappeared and the eosinophile count in the blood returned to normal. Exposure of these recovered patients to their supposedly important allergic factors did not result in a renewal of their attacks. Wittkower and Petow state that whether psychic factors play the rôle simply of one of many conditioning factors in the development of asthma, or whether asthma in a greater or lesser number of cases is to be

considered an organ-determined psychoneurosis, is a matter for discussion. The precipitation of single attacks by psychic influence in already established asthma has been known for a long time, since Hippocrates, and is not difficult to explain. The affect is discharged over the vegetative nervous system and mobilizes the mechanism already established, but the beginning of the asthma also is frequently preceded by violent psychic excitement. Emotions undoubtedly play a considerable rôle in the persistence of asthma. Since, however, many individuals live through violent emotional experiences without becoming neurotic or developing asthmatic attacks they cannot conceive of a purely affect-dynamic causation of neuroses or asthma. It is necessary to assume that the precipitating affect finds a psychic and probably also a somatic preparedness. They were interested in the relations between psychic and allergic mechanisms. It was found that although the patient's symptoms could be definitely affected by psychotherapy, a demonstrable allergic skin reaction could not be produced by hypnotic suggestion nor could an allergic skin reaction be eliminated by suggestion. Their concept of the psychogenesis of asthma was summarized as follows: (1) An allergic genesis of asthma without a neurotic component is certainly valid in many cases. (2) A pure psychogenesis without somatic predisposition is possible in itself, in many cases even probable, but unproved. (3) The vast majority of cases are doubly determined, whether it be that psychic factors in the presence of an allergic predisposition mobilize the latent tendency to illness, or whether it be that an allergic asthma becomes established secondarily in a neurotic superstructure.

In stressing the importance of affective disorders many other illustrations might be chosen from the studies on psycho-somatic relationships in reference to all the organ systems. The internist reviewing this literature already so helpfully prepared by Dunbar will, I feel sure, be surprised at the extent of these studies and perhaps shocked by some of the extreme views presented. Just how closely or how far away we follow these suggestions is just now, I think, not so very important. It is important that we consider them, that we give them a careful hearing or reading. A closer association with conservative psychiatrists may be helpful both to us and to our patients. We should at least be willing to admit that emotions can and frequently do cause changes in bodily functions, and be willing, when studying an ill patient, to follow Bleuler and ask the question, "To what extent physical and to what extent psychic?"

REFERENCE

- DUNBAR, H. F. Emotion and bodily changes. A survey of literature on psychosomatic interrelationships, 1910-1933. Columbia Univ. Press, New York, 1935, 595 pp.

STUDIES ON THE LIFE HISTORIES OF PATIENTS WITH CHRONIC ULCERATIVE COLITIS (THROMBO-ULCERATIVE COLITIS), WITH SOME SUGGESTIONS FOR TREATMENT¹

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Two types of colitis in which intestinal ulceration occurs have long been recognized as entities, that is, tuberculous colitis and amebiasis. Until 1924, all other types of colitis were unconditionally assigned to the category of idiopathic or nonspecific colitis. There was a time after this when some felt that all cases denominated "idiopathic" or "nonspecific" were of streptococcal origin. It was thought that when the specific streptococcus was not isolated, the cause lay largely in the shortcomings of bacteriologic technic. As time went on, however, it became increasingly apparent that not all the cases laboring under the undescriptive term "chronic ulcerative colitis" were of one type. In the light of accumulated knowledge, reclassification of individuals who had ulcerative colitis seemed urgent. As the necessity of this became more and more apparent, we were faced with the question of where and when to start such a classification. Those of us who were especially interested in the lower segments of the gastrointestinal tract decided, on January 1, 1936, that thereafter we would divide all cases formerly laboring under the designation "chronic ulcerative colitis of nontuberculous and nonamebic origin," into three groups, that is, group 1, group 2 and group 3. In group 1 we placed those patients who presented the typical clinical, proctoscopic and roentgenologic picture encountered in chronic ulcerative colitis of the streptococcal variety. In group 3 we placed those who presented an atypical proctoscopic and roentgenologic picture and in group 2, those who did not give proctoscopic evidence of ulcerative disease of the rectum but who did give roentgenologic evidence of such disease. This separation into groups was made only for the sake of convenience and in the hope that something further might be learned about the etiology of groups 2 and 3, as well as for the purpose of trying to establish more adequate therapy.

Two years of this arbitrary classification prompted a review of a series of cases which came under our care after establishment of the importance of the streptococcus as an inciting factor in some of these cases. We felt that the establishment of a pattern of the life history of patients with chronic ulcerative colitis of the streptococcal variety might serve as a guide in our future classification and treatment of this intractable disease. Consequently

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we began our studies with the year 1925. In the years 1925 to 1931 inclusive the histories of 1000 of the patients registered at the clinic were filed under the heading, "chronic ulcerative colitis." In the same period, 73 patients who had tuberculous ulcerative colitis were studied and approximately 500 patients who had amebiasis, or infection with *Endamoeba histolytica*, were encountered. During these same years, many more cases in which the diagnosis was "mucous colitis" or "irritable bowel" were observed. Parenthetically, it may be said here that our present knowledge of function and disease of the intestine makes the term "mucous colitis" no longer tenable.

Recently the methods of following up patients by the medical profession have been challenged and this challenge served as a further stimulus to a very detailed statistical study and follow-up of these cases. Careful analysis of the 1000 records revealed that only 871 of the patients belonged in group 1, that is, in the group which presented typical clinical, proctoscopic, and roentgenologic features. The other 129 were of groups 2 and 3. It is our conviction that it is cases of the type of these 129 that have confused our knowledge of the etiology of bacterial ulcerative colitis. If the term "idiopathic" is to be used at all, it should be applied to the cases belonging to the groups to which this 129 belong. However, to encourage more intensive study of these and to discourage their glib acceptance as idiopathic or nonspecific, the term should be replaced by the designation "of unknown etiology." Buie and one of us (Bargen) have studied the inception, bacteriology, and pathology of chronic ulcerative colitis of the streptococcal type and feel that the term "thrombo-ulcerative colitis" can be suitably applied to this group of cases.

We have then tuberculous, amebic, and thrombo-ulcerative colitis, and ulcerative colitis of unknown etiology. This review is concerned specifically with the 871 patients who presented typical clinical, proctoscopic and roentgenologic evidence of a disease of bacterial etiology. The 871 cases will, henceforth in this presentation, be designated as cases of "thrombo-ulcerative colitis." Our study brought out the fact that the course and prognosis of this disease varied both as regards age of the individual afflicted as well, in many instances, as sex. Four hundred and ninety-one were males and 380 were females. Some of the tables that accompany this paper contain material which is not immediately called for by the relevant text, but since inclusion of such material does not obscure the points brought out, and since it is believed to add to the value of the report as a whole, it is supplied.

The native habitat of these patients is of some interest. Most of the states of the Union, except a few of the Southern states, were represented, for example, no patients in this series came from Florida, Georgia, the Carolinas, or Arizona. In nearly every instance, except Minnesota, the percentage of patients from the various states who had colitis, was greater than the percentage of patients of the clinic as a whole who came from these

states In recent years 32 per cent of The Mayo Clinic patients have come from Minnesota Only 12 per cent of the patients who had colitis came from Minnesota On the other hand, 12 per cent came from Iowa, 12 per cent from Illinois, 7 per cent from Wisconsin, 5.5 per cent from New York, and 8 per cent from the various provinces of Canada, whereas registration at the clinic from these regions is 9, 9, 6, 0.8 and 5 per cent respectively The rest of the patients come from widely separated regions of the United States and other countries, a few from Mexico, Panama, Puerto Rico, Peru and the South Sea Islands

In many cases definite factors predisposing to the disease could be elicited (table 1) It will be seen from this table that such factors could definitely

TABLE I
Predisposing Factors in the Development of Thrombo-Ulcerative Colitis, Patients

Factor	Age at onset, years								Total
	Males				Females				
	0-9	10-19	20-29	30-74	0-9	10-19	20-29	30-74	
Upper respiratory infection	3	16	20	26	2	13	15	13	108
Childhood diseases	3	—	1	—	2	1	—	1	8
Dietary indiscretion	1	2	4	11	—	1	3	2	24
Physical and mental fatigue	—	4	6	6	—	2	5	6	29
Rectal surgery	—	—	4	6	—	2	2	3	17
Abdominal surgery	—	—	1	2	—	2	1	5	11
Trauma	1	1	1	2	—	1	—	—	6
Drastic catharsis	—	—	3	3	—	2	3	5	16
Foci with sepsis	—	1	3	1	—	2	3	3	13
Exposure	—	1	17	4	—	3	7	6	38
Dysentery epidemics	1	1	—	1	—	—	2	2	7
Pregnancy	—	—	—	—	—	3	17	7	27
Undetermined	10	49	109	167	9	35	89	99	567
Total	19	74	169	229	13	67	147	153	871

be elicited in 304 instances Upper respiratory infections included tonsillitis, pneumonia, influenza, and otitis media Foci of infection, with sepsis, were represented by mastoiditis, neisserian infection, and incomplete abortion Pregnancy included those which went to term as well as those which were terminated by induced or spontaneous miscarriages "Physical and mental fatigue" refers to unusual worry, the shock of a death in the family, and symptoms of menopause It will be noted that the condition followed epidemic dysentery in only seven instances The factors influencing relapse of the disease, once controlled, closely parallel those associated with the first attack (table 2)

It has been thought by some that this disease always begins in an insidious manner and that those cases which start with severe, or even ful-

TABLE II
Factors Influencing Relapses in Thrombo-Ulcerative Colitis, Patients

Factor	Age at Onset, Years								Total
	Males				Females				
	0-9	10-19	20-29	30-74	0-9	10-19	20-29	30-74	
Upper respiratory infections	5	16	25	39	1	16	15	17	134
Childhood diseases	—	1	—	—	3	—	—	—	4
Dietary indiscretion	—	—	5	—	—	—	2	3	10
Physical and mental fatigue	1	4	3	—	—	7	8	3	26
Foci with sepsis	—	2	14	8	—	3	6	3	36
Dysentery epidemics	—	1	—	—	—	1	—	—	2
Pregnancy	—	—	—	—	—	1	6	1	8
Indeterminate infection	1	—	—	—	—	—	—	—	1
Undetermined	12	50	122	182	9	39	110	126	650
Total	19	74	169	229	13	67	147	153	871

minating, bloody, purulent dysentery are not instances of the same condition. For convenience, we divided the cases into three types on the basis of early symptoms. In those cases in which the illness began with passage of one or more bloody, rectal discharges, without other apparent symptoms, the onset was said to be "insidious." If the condition began with sudden, severe, bloody dysentery but otherwise without symptoms of sepsis and toxemia, the onset was said to be "severe." If violent, bloody, purulent dysentery, with septic type of fever, great toxemia and rapid depletion were the elements of the initial episode, the onset was said to be fulminating (table 3).

TABLE III
The Character of the Onset of Symptoms in Thrombo-Ulcerative Colitis, Patients

Age at Onset, Years	Males				Females			
	Insidi-ous	Severe	Fulmi-nating	Total	Insidi-ous	Severe	Fulmi-nating	Total
0-9	7	9	3	19	5	5	3	13
10-19	34	33	17	84	25	28	14	67
20-29	84	52	33	169	83	40	24	147
30-74	117	73	39	219	89	34	30	153
Total	242	157	92	491	202	107	71	380

The manner of progression of this disease was carefully studied and its clinical course could readily be classified into eight types (table 4). Types 7 and 8 deserve particular comment. The illness of 41 males and of 11 females remained mild for months or years and then suddenly changed to

TABLE IV

The Manner of Progression of Thrombo-Ulcerative Colitis, Patients

Manner of Progression	Age at Onset, Years									
	Males					Females				
	0-9	10-19	20-29	30-74	Total	0-9	10-19	20-29	30-74	Total
1 Mild throughout entire course	—	10	28	48	86	2	4	31	34	71
2 Intermittent with declining severity	4	21	23	41	89	2	6	13	29	50
3 Septic course with complete recovery	—	2	11	10	23	1	7	9	4	21
4 Constant without remission	—	4	7	11	22	—	9	18	20	47
5 Slowly progressive without remission	4	7	32	46	89	4	6	24	20	54
6 Intermittent with progressive severity	7	17	55	49	128	1	30	47	40	118
7 Insidious onset with slow progression, changing to fulminating course and ending fatally	4	11	8	18	41	3	2	5	1	11
8 Fulminating course throughout, ending fatally	—	2	5	6	13	—	3	—	5	8

a progressive, fulminating affair which ended fatally in spite of all therapeutic attempts, medical or surgical. That of 13 males and 8 females began as a violent fulminating disorder and progressed rapidly to fatality.

In a previous study² of the cause of relapses of thrombo-ulcerative colitis, the fact was brought out that relapses occurred more commonly during the months when upper respiratory infections were particularly prevalent than during other months. Hence, an effort was made to determine the month of onset of the symptoms. Only positive data were recorded. One might be inclined to deduce from this that June and October were the least likely months for invasion by this disease (table 5). Our clinical impression would thus be substantiated but we feel that larger series of cases should be accurately followed before such a deduction were drawn. This feature is being carefully observed in current cases. In this series of cases, positive data were at hand in only 627.

In several previous series of cases of ulcerative colitis, complications of these conditions were studied.¹ This is the first series of this size in which the study was limited strictly to thrombo-ulcerative colitis. It will be noted that 42 per cent of the males and 40 per cent of the females had complications of one form or another (table 6). It will also be seen that 20 per cent of the complications of males, but only 11 per cent of the complications of females, were multiple. This would tend to stress the observation that

TABLE V
Month of Onset of Thrombo-Ulcerative Colitis

Month	Patients		
	Males	Females	Total
January	36	16	52
February	29	16	45
March	22	14	36
April	23	9	32
May	20	16	36
June	15	10	25
July	22	18	40
August	22	15	37
September	23	14	37
October	14	11	25
November	23	12	35
December	19	16	35
Indeterminate	223	21	244

TABLE VI
Complications and Sequelae of Thrombo-Ulcerative Colitis among Children and Adults

Complication	Males			Females		
	Children	Adults	Total	Children	Adults	Total
Polyposis	48	42	90	7	44	51
Stricture	7	46	53	3	42	45
Perianal abscess-fistula	4	39	43	2	28	30
Arthritis	4	23	27	4	24	28
Erythema nodosum	1	4	5	—	4	4
Pyoderma gangrenosa	—	3	3	—	1	1
Perforation	1	6	7	—	3	3
Liver abscess	—	2	2	—	2	2
Carcinoma	5	14	19	1	8	9
Phlebitis	—	1	1	1	—	1
Iritis	—	3	3	—	2	2
Deafness	1	—	1	—	—	—
Splenomegaly	2	—	2	—	—	—
Nephritis	—	9	9	1	2	3
Psychosis	—	6	6	—	3	3
Massive hemorrhage	1	1	2	—	2	2
Endocarditis	1	3	4	—	5	5
Kidney stones	—	4	4	—	4	4
Multiple complications	10	80	90	7	35	42
Total individuals with complications	24	185	209	15	136	151

the disease may attack males more violently than it attacks females. Perhaps the reason for this may be found in the fact that the occupations of men lie more in the fields wherein upper respiratory infections and trauma are prevalent (tables 1 and 2)

The tendency for individuals who develop the conditions which we have called complications is for them to have more than one. Actually several

individuals have been known to have six or more of these. The unusually high incidence of carcinoma occurring in the course of this disease is worthy of mention. Every one of these patients was observed for years before carcinoma developed. In each instance, it was ushered in by a noteworthy change in symptoms. The carcinomas had a tendency to be multiple. In six instances, the patients were children whose disease began before the age of 10 years, five of these were boys. Death in these cases occurred between the ages of 15 and 25 years, and the downward course after first symptoms of carcinoma appeared was exceedingly rapid and in no instance lasted more than a few months. The incidence of carcinoma in the total group was 3.2 per cent. The incidence of carcinoma of the intestine as a factor in mortality, according to the United States Department of Commerce for 1923 to 1929 inclusive was 0.011 per cent. The incidence of carcinoma of the large intestine among patients of the clinic during these years was 0.88 per cent. These observations would point to one direction that the search for the cause of carcinoma might take.

Another point of particular note in table 6 is the fact that only four patients had liver abscess. When one thinks of the vascular drainage of the intestine, this becomes the more striking. It is also striking in its contrast to the cases of amebiasis, wherein liver abscess is the most common complication. A point of interest in this regard is the fact that in eleven of these cases, in seven of which the patients were men and in four of which they were women, a duodenal ulcer occurred in association with the thrombo-ulcerative colitis.

A fair index of the severity of this disease in any given case can be obtained by study of the extent of the damage that has been inflicted on the bowel. This is best done by roentgenologic study, through retrograde filling of the colon with an opaque substance, and by the double-contrast method of examination. By these methods it was learned that in the majority of these 871 cases most of the large intestine became involved by the ulcerative process (tables 7 and 8). In 400 of the cases, 232 males and 168 females, the entire large intestine was involved when the patients were first examined. In 30 of these cases, 16 males and 14 females, the entire large intestine and terminal part of the ileum were affected. In 47 more cases the disease progressed between subsequent observations so that the entire large intestine became involved. In 558 cases (325 males and 233 females) only the one diagnostic roentgenologic examination of the large intestine was made. Although it is unwise to subject the intestines of these individuals to any avoidable trauma, yet in recent years it has been possible to make more observations per individual and hence the number of cases in which complete regression of the disease is known to have taken place has been greatly increased. Nevertheless, 16 males and 12 females of this group had lost all signs of the disease, as determined by proctoscopic and roentgenologic examination, at the time of subsequent observations. It is safe to assume that in many of the cases in which, in later tables (namely,

TABLE VII

Extent of Involvement of the Intestine by the Lesions of Thrombo-Ulcerative Colitis among Males, Demonstrated Roentgenologically

Age at Onset, Years	Total Patients	Extent of Involvement on Admission *					Single Observation	Subsequent Observations				
								No Change	Progression of Disease		Regression of Disease	
		1	2	3	4	4+			Slight	Marked	Slight	Complete
0-4	8	1	—	2	3	2	7	1	—	—	—	—
5-9	40	7	1	2	28	2	28	7	1	3	—	1
10-19	132	32	16	12	66	6	85	23	12	5	2	5
20-29	151	49	24	12	63	3	106	24	10	6	2	3
30-74	160	66	28	4	56	3	99	32	10	7	4	7
Total	491	155	69	32	216	16	325	87	33	21	8	16

* Involvement from rectum to sigmoid, 1, from rectum to splenic flexure, 2, from rectum to hepatic flexure, 3, entire colon, 4 and entire colon and terminal ileum, 4+

TABLE VIII

Extent of Involvement of the Intestine by the Lesions of Thrombo-Ulcerative Colitis among Females, Demonstrated Roentgenologically

Age at Onset, Years	Total Patients	Extent of Involvement on Admission *					Single Observation	Subsequent Observations				
								No Change	Progression of Disease		Regression of Disease	
		1	2	3	4	4+			Slight	Marked	Slight	Complete
0-4	4	—	—	—	3	1	2	2	—	—	—	—
5-9	28	3	1	4	17	3	19	5	1	2	—	1
10-19	127	35	16	11	60	5	81	31	5	5	4	1
20-29	124	50	17	12	42	3	70	24	12	10	3	5
30-74	97	36	16	11	32	2	61	17	3	9	2	5
Total	380	124	50	38	154	14	233	79	21	26	9	12

* Involvement from rectum to sigmoid, 1, from rectum to splenic flexure, 2, from rectum to hepatic flexure, 3, entire colon, 4 and entire colon and terminal ileum, 4+

tables 12 and 13) the patients are referred to as symptom-free, the same happy state of affairs is present, for represented among these are many patients free from all symptoms or signs of the disease for from 7 to 14 years. Tables 7 and 8 serve to give a broad view of the method of progression of this disease as observed roentgenologically.

There is no more impressive manner of emphasizing the serious nature of this disease than by study of tables of mortality. This is a study of the

life histories of patients who had thrombo-ulcerative colitis, hence, the immediate as well as the later mortality is discussed. All the deaths which occurred in the period of 14 years were considered. Among the patients treated medically, 284 males and 211 females, 81 had died before March 1, 1938. Of these, 13 had died from causes unrelated to the intestinal disease, the causes of their deaths, with the exception of one from suicide, were largely those generally associated with changes of old age, that is, apoplexy and other forms of vascular change. Twenty-eight died of conditions in which the major causes of death were not ulcerative colitis, but its presence was, more than likely, contributory (table 9). Forty died of the disease

TABLE IX
Mortality among Patients Treated Medically

Cause of Death	Males			Females		
	Children	Adults	Total Deaths	Children	Adults	Total Deaths
Carcinoma of rectum	1	1	2	—	—	—
Nephritis	1	1	2	—	2	2
Pneumonia	—	2	2	—	2	2
Hemorrhage	—	2	2	—	1	1
Lung abscess	—	1	1	—	—	—
Liver abscess	—	2	2	—	—	—
Perforation of colon	—	5	5	—	1	1
Inanition	—	3	3	—	1	1
Thrombo-ulcerative colitis and ex- ophthalmic goiter	—	—	—	—	1	1
Thrombo-ulcerative colitis and large perirectal abscess	—	—	—	—	1	1
Thrombo-ulcerative colitis	7	28	35	—	5	5
Death unrelated to colonic disease	—	9	9	—	4	4
Total	9	54	63	—	18	18

without other complicating cause. The mortality among patients who were subjected to operation is reviewed in table 10. Among the 871 patients, 175 underwent some form of abdominal surgical intervention for attempted relief of the colitis, its complications, or other unrelated abdominal pathologic conditions. Seventy patients were operated on at the clinic. The multiplicity of surgical maneuvers is indicated in table 10. One individual underwent the following operations: cecostomy, colostomy three times, closure of the colonic stoma three times and ileostomy. Several individuals underwent ileostomy and ileosigmoidostomy at different times, or ileosigmoidostomy followed by ileostomy. Forty-two of the patients had been subjected to appendicostomy, cecostomy, or colostomy before their first examination at the clinic. Our study would suggest that appendicostomy and cecostomy fall far short of their desired effect. In this series of cases they rarely relieved, and never resulted in abatement of, intestinal symptoms

Patients who had undergone a total of 125 surgical procedures were living March 1, 1938, of these, 27 patients stated that they were well, the intestinal symptoms of all the others have continued

The causes of death are given in table 11 This portion of our study

TABLE X
Mortality among Patients Treated Surgically

Procedure	Operations *			Outcome			
	Total	Adult	Children	Living		Dead †	
				No	Per cent	No	Per cent
Appendicectomy	10	7	3	10	100	—	—
Appendicostomy, cecostomy, colostomy	49	47	2	41	83	8	17
Ileostomy	98	86	12	60	62	38	38
Colectomy	10	10	—	7	70	3	30
Ileocolostomy	12	11	1	4	33	8	67
Closure of ileac stoma	1	1	—	—	—	1	100
Resection for carcinoma	1	1	—	—	—	1	100
Other abdominal surgery	11	9	2	3	27	8	73
Total	192	172	20	125	66	67	34

* Of these surgical procedures, 87 were performed at The Mayo Clinic and 105 elsewhere. Of the latter, 62 were carried out before the patient came to the clinic the first time. If one individual underwent more than a single operation, each operation was entered once, 175 individuals underwent the 192 operations listed. Ileocolostomy includes ileosigmoidostomy.

† Deaths include those which occurred in hospital. If a patient underwent several operations, death was listed against the last operative procedure.

TABLE XI
Causes of Death of Patients Treated Surgically 106 Males and 69 Females

Cause of Death	Males			Females		
	Total Deaths	Children	Adults	Total Deaths	Children	Adults
Peritonitis	14	1	13	8	1	7
Embolism	2	—	2	—	—	—
Inanition	3	—	3	—	—	—
Pneumonia	1	—	1	—	—	—
Carcinoma	11	5	6	5	1	4
Obstruction	3	1	2	2	—	2
Multiple liver abscess	1	—	1	—	—	—
Addison's disease	—	—	—	1	—	1
Died elsewhere immediately after making of stoma	4	1	3	—	—	—
Died elsewhere later after making of stoma	5	1	4	7	—	7
Total	44	9	35	23	2	21

further emphasizes the very serious nature of this disease and suggests very strongly that surgery should be limited to complications

The disease is particularly ravaging among children in the first decade of life and responds relatively poorly to present forms of treatment (tables 12 and 13) After the first decade of life, response to treatment is increasingly more favorable The outlook among children who have suffered severely from this disease is rather gloomy In general it can be said that the older the individual afflicted, the better the outlook for recovery

TABLE XII

End Results of Treatment of 491 Male Patients with Thrombo-Ulcerative Colitis Observed for Seven to Fourteen Years

Age at Onset, Years	Total Number	Results												
		Symptom Free		Good		Satisfactory		Good Progress, Per cent of Cases	Unsatisfactory		Dead at Time of Inquiry			
											Total		Cancer	
		Number	Per cent	Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent	Number	Per cent
0-9	19	5	26.3	4	21.0	3	15.8	64	7	36.8	6	31.6	5	26.3
10-19	74	28	37.8	15	20.3	10	13.5	72	21	28.4	14	18.9	4	5.4
20-29	169	69	40.8	32	18.9	34	20.1	78	34	20.1	26	15.4	2	1.2
30-74	229	98	42.8	34	14.8	32	14.0	76	65	28.4	49	21.4	3	1.3
Total	491	200	40.7	85	17.3	79	16.1		127	25.9	95	19.3	14	2.8

TABLE XIII

End Results of Treatment of 380 Female Patients with Thrombo-Ulcerative Colitis Observed for Seven to Fourteen Years

Age at Onset, Years	Total Number	Results													
		Symptom Free		Good		Satisfactory		Good Progress, Per cent of Cases	Unsatisfactory		Dead at Time of Inquiry				
											Total		Cancer		
		Number	Per cent	Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent			
0-9	13	3	23 1	4	30 8	2	15 4		69	4	30 8	3	23 1	1	7 7
10-19	67	20	29 8	9	13 4	14	20 9	64	24	35 8	11	16 4	—	—	
20-29	147	63	42 8	19	12 9	29	19 7	76	36	24 5	15	10 2	3	2 0	
30-74	153	60	39 2	34	22 2	22	14 4	76	37	24 2	20	13 1	6	3 9	
Total	380	146	38 4	66	17 4	67	17 6		101	26 6	49	12 9	10	2 6	

The principles of treatment worked out for each of these different types of ulcerative colitis have been fairly well standardized

In the cases of amebiasis or amebic colitis, chemotherapy plays the major rôle. The effort is to eradicate the *Endamoeba histolytica* and promote healing of the diseased bowel. The drugs in common use have been principally three: ipecac and its derivative, emetine hydrochloride, arsenic in the form of stovarsol, the methenamine derivative of meta-amino-paroxyphenylarsenic acid (treparsol), or carbarsone, and complex products of iodine, that is, vioform, iodoxy-quinoline sulphonic acid (anayodin), chiniofon, and the like. Promotion of intestinal rest is indicated in all types of ulcerative colitis.

Whenever the diagnosis of tuberculous colitis is established, the place for the patient is a sanatorium or a similar place devised for the care of the tuberculous.

A well-ordered program for the care of the patient with thrombo-ulcerative colitis includes the administration of serums and vaccines directed against the offending streptococcus, a diet rich in calories, high in proteins, and low in residue, frequently a series of transfusions of small amounts of blood (200 to 250 c c at a time), removal of foci of infection, good nursing care, adequate rest of the bowel and other symptomatic measures. Chemotherapy has a very small place in the management of this disease. Innumerable drugs have been used in the hope that some "quick cure" might be found. We shall mention only a few that have been tried and found wanting. Calcium and parathyroid extract had their day, their usefulness is negligible in this condition. Arsenic does great harm in many of these cases. Azochloramid has had its advocates recently. As a local application, it causes much intestinal irritation. Kaolin and aluminum hydroxide for rectal instillation serve only to soothe the rectum in some of the milder cases. Histidine hydrochloride apparently has a small field of usefulness in a few cases. The recent furor about sulfanilamide and allied drugs naturally led to its trial in cases of this infection. Results with it can be summarized about as follows. In a few of the milder cases, with involvement of distal segments of the bowel alone, striking improvement has followed its administration.⁴ In most of them no apparent effect was achieved. In any event, these are not the cases wherein help is greatly needed. Progress in these cases, under the program mentioned above, is satisfactory. It is in the severe cases of fulminating disease that we are groping for help. In them, the sulfanilamide group of drugs so far has not proved of value, because the margin between safety and toxicity is not great. In four cases in which patients who had received these drugs came under our observation, hepatitis with jaundice was encountered, in three cases the patient died and in another one peripheral neuritis developed.

Many medicines have been tried in an attempt to control this disease. So far no single drug has offered much help for more than a few patients. Many have been misled by the apparent brilliant results achieved by single

therapeutic agents in a few cases. Careful analysis of these results invariably has revealed that the cases were mild and that involvement was only of distal segments of intestine. Probably the most important factor in the treatment of these cases was rest.

Solution of the whole therapeutic problem depends on better understanding of this infection. Let it be remembered that the infection is destructive, progressing, in many respects similar to tuberculosis, and therefore let a program of management for its control be adopted, search for a "miraculous cure" should not be continued. The keynote of the program should be the attempt to reverse a devastating and destructive infection. The patient must adopt the philosophy of life that the patient with peptic ulcer is supposed to have.

Quite a different situation exists in the group of 129 cases of unknown etiology. Some of these cases are, more than likely, of the nature of the end results of a state of deficiency. Vitamin concentrates and vitamin therapy in general have afforded striking relief in some of them. Here trial of the various therapeutic aids advocated from time to time seems justified.

SUMMARY

During the years 1925 to 1931 inclusive, 73 patients who had tuberculous ileocolitis, approximately 500 who had amebic colitis, 129 who had ulcerative colitis of undetermined etiology, and 871 who had thrombo-ulcerative colitis were observed at The Mayo Clinic. A chiefly statistical study was made of the records of the 871 patients who had thrombo-ulcerative colitis. It tells the story of patients who have been followed from 7 to 14 years after first observation. All ages recorded in the paper concern the age of onset of symptoms of the disease.

Predisposing factors and factors affecting relapses of the disease are chiefly the following: upper respiratory infection, disease of childhood, dietary indiscretion, physical and mental fatigue, rectal or abdominal surgical operation, trauma, drastic catharsis, foci of infection with sepsis, exposure, dysentery epidemics, and pregnancy.

This disease may begin in an insidious manner. Again, it may come on suddenly, as a violent diarrhea without toxic symptoms, or it may start in a fulminating fashion, associated with marked toxemia, fever and all the concomitants of a severe septic process.

On the basis of its course, the disease can be readily divided into the following types: (1) mild throughout, (2) intermittent with declining severity, (3) septic with complete recovery, (4) constant without remission, (5) slowly progressive without remission, (6) intermittent with progressive severity, (7) insidious onset with slow progression, changing to a fulminating condition and ending fatally and (8) fulminating throughout, ending fatally.

The major complications and sequelae of thrombo-ulcerative colitis include polyposis, stricture, perianal abscess-fistula, arthritis, erythema nodosum, pyoderma gangrenosa, perforation, liver abscess, carcinoma, phlebitis, iritis, deafness, splenomegaly, nephritis, psychosis, massive hemorrhage, endocarditis and kidney stones

There is no special time of year in which this disease begins but it is of interest to note that more of the cases had their onset in January, February, or July than in the other months of the year

The progress of the invasion from the rectum toward the cecum is indicative of the destructive nature of the disease. This is best observed by the roentgenologist. The mortality associated with this destructive infection emphasizes its serious nature.

Surgical intervention in this disease should be limited to complications and sequelae. Some of these demand wisely chosen surgical measures, both from the standpoint of the time of their application and from that of the lesion present. An individual afflicted with thrombo-ulcerative colitis presents a poor surgical risk if a surgical attempt must be made to relieve another intercurrent abdominal pathologic condition.

The end results of this infection may be devastating but it may also end in complete relief of all symptoms and signs of intestinal pathologic change. This happy result occurs frequently enough to make it urgent that a well-ordered regimen be followed without deviation by these patients for months and years.

REFERENCES

- 1 BARGEN, J A. The management of colitis, 1935, National Medical Book Company, Inc., New York, 233 pp
- 2 BRUST, J C M, and BARGEN, J A. The neoplastic factor in chronic ulcerative colitis, *New England Jr Med*, 1934, cc\, 692-696
- 3 BUIE, L A, and BARGEN, J A. Chronic ulcerative colitis a disease of systemic origin, *Jr Am Med Assoc*, 1933, cl, 1462-1466
- 4 BANNICH, E J, and BROWN, A E. *Jr Am Med Assoc* (unpublished)

QUININE AND ATEBRINE—A COMPARISON

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To be tremendously over-rated when first introduced is quite a characteristic event in the history of all new remedial agents—especially of specifics. Then after the pendulum has swung in the opposite direction through the condemnations of the ultra-conservatives a return towards a correct estimate of the remedial measure may be expected.

Practically ever since the historical occasion when a decoction from the bark of a Peruvian tree first effected a spectacular cure in the oft-cited case of Cinchona, the wife of the Spanish Viceroy to Perú, substitutes for this bark and its derivatives have been eagerly sought because of the many disagreeable features which attend a thorough treatment with cinchona and its alkaloids. Among the disadvantages are the lengthy periods of treatment which are necessary, the disagreeable bitterness of the drug, the *tinnitus aureum*, the general malaise produced by the drug alone, the reputed action on the pregnant uterus, the occasional deafness and amblyopia attending intensive treatment, the economic disadvantage of prolonged disability, and the serious anaphylactic-like complications which occasionally are noted when idiosyncrasies exist.

We who are particularly interested in tropical medicine were so often disappointed with the various substitutes for quinine which appeared on the market from time to time—especially such as stovarsol and that inglorious panacea namely intravenous mercurochrome—that plasmochin and atebrine were tried out with some reluctance at first by many investigators. The value of plasmochin as a gametocide soon, however, became appreciated, and many of us were most favorably impressed with its application as a sanitary measure in some of our United Fruit Company Divisions where it undoubtedly reduced our malarial index quite remarkably. As evidence of this I refer to the several annual reports of the Medical Department of the United Fruit Company from 1926 to 1931. Atebrine was brought out later, and in that its action was reported to be directed specifically against asexual forms only of the parasites, it appeared that it might possibly be used as a substitute for quinine, and accordingly be given successfully in conjunction with plasmochin. The important consideration then was to determine the comparative values of quinine and atebrine. I do not intend to review the results of the extensive investigations that have already been reported but it is worthy of mention that these indicate that in the last analysis some writers still prefer quinine while other enthusiasts extoll atebrine and welcome it eagerly as a substitute for the older therapeutic agent. Our in-

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vestigation in this hospital was purely of a practical nature and, due to lack of certain facilities, we did not attempt the type of research reported by Manson-Bahr and Walters in the *Lancet* of January 6, 1934, but rather groped along lines of study to determine which drug, in the main, might be more practical for our use in the various Divisions of our Company where often rather unusual conditions prevail.

The holdings of the Magdalena Fruit Company extend from the Port, namely Santa Marta, a city of some 25,000 inhabitants and incidentally the oldest town built by foreigners in the entire Western Hemisphere, inland some 70 miles to the farthest banana farms. This torrid littoral, which slopes from Andean heights of perennial snow towering over 19,000 feet, is so dry that the farm lands require irrigation during the months principally from December to April. The heaviest rainfall occurs usually during the months of October and November. In table 1 is the rainfall report which was kindly submitted by the Agricultural Department.

TABLE I
Average Division Rainfall in Inches

Year	1928	1929	1930	1931	1932	1933	1934	1935
January						06	18	
February			01	08				72
March	57	80	63	1 73	10	38		07
April	70	1 89	3 21	4 96	5 59	1 07	1 40	1 84
May	6 74	3 31	3 16	10 12	6 69	9 20	9 01	7 12
June	5 95	6 27	4 48	9 36	5 83	6 46	9 92	7 68
July	1 80	3 36	2 28	16 40	6 43	6 81	1 47	4 54
August	7 99	4 39	3 97	2 38	9 68	11 05	2 58	11 75
September	8 69	5 28	4 71	10 94	11 13	13 48	2 61	5 82
October	7 79	15 76	6 16	8 36	18 39	11 91	15 65	8 53
November	8 39	2 95	50	9 40	13 61	17 50	5 82	
December	03		10	80	74	1 90	2 10	
Year	48 75	44 01	29 21	74 52	78 14	79 88	50 70	

(Note: 1928 and 1929 include Rio Frio.)

The relation between rainfall and malarial infection during the various months can be determined by reference to the tabulations of hospital admissions (table 2).

Our medical staff consists of seven physicians, four of whom constitute the staff of the Santa Marta Hospital (an institution of about 100 beds at this time), the other three being stationed in various dispensaries in the farming districts. The milder cases of malaria are treated in the dispensaries while only the more serious cases, or cases where malaria is found as a secondary diagnosis during the routine physical and laboratory examinations, are treated in the hospital. When we arranged to attempt this investigation, it was decided that all cases which were admitted to the hospital with malaria as either a primary or secondary diagnosis, would be included in this series and that there would be absolutely no selection of cases for

either drug Accordingly, the first 10 cases were treated with atebine and the second 10 with quinine Thus after each group of 10 cases the treatment was alternated until a series of 200 cases was completed, 100 with quinine and 100 with atebine Sixteen and one-half months were required to complete this series, that is from July 1, 1934 to November 15, 1935 when the last case of the series appeared The distribution of these cases by months is shown in table 2

Of these cases only six were below the age of 12 years, of the others, 169 were men and 25 women

Some of the smears were reported as "mings and tertian" These were classed as tertian and not as mixed infections It chanced that in the atebine

TABLE II

	Estivo-Autumnal	Tertian	Quartan	Mixed	Total Cases
1934					
July	4	2	1	—	7
August	6	2	—	—	8
September	—	1	—	—	1
October	4	1	—	EA & Q 1	6
November	11	8	1	—	20
December	16	11	2	—	29
1935					
January	19	10	3	EA & Q 1	33
February	14	2	2	—	18
March	11	3	3	—	17
April	6	1	—	—	7
May	2	3	—	—	5
June	2	1	4	—	7
July	8	7	—	—	15
August	4	2	1	—	7
September	3	3	1	—	7
October to Nov 15	8	3	—	—	11
	2	—	—	—	2
	120	60	18	2	200

series 63 were estivo-autumnal cases, 31 tertian and 6 quartan while the quinine group contained 57 estivo-autumnals, 29 tertians, 12 quartans and 2 mixed infections of quartan and estivo-autumnal

In every case of each series, one plasmochin compound tablet was administered every night as this, in earlier research studies, was found to be quite sufficient for complete gametocidal effect

In the discussion of dosage in this article, the tablet will be given as the unit in order to make better comparisons regarding the costs of the different drugs The quinine tablet contained 5 grains or 0.33 gram, the atebine tablet, 1.5 grains or 0.1 gram, and the plasmochin compound tablet containing quinine 0.125 grams, and plasmochin 0.01 gram

In the series of 200 cases three resulted in death, in each of which malaria

was only a contributory cause, one, a Scotchman having been admitted to the hospital with lobar pneumonia, and the other two having succumbed to cardio-renal disease with broken compensation. Two of these, the lobar pneumonia case and one of the cardio-nephritics, happened to have belonged to the quinine group while the third received atebrine treatment for the co-existing malaria. The last named case had completed his atebrine course several weeks before his death, for which the drug therefore could hardly be held responsible. One patient of the atebrine series completed his course of therapy but was discharged by mistake before his blood and urine specimens were rechecked.

All atebrine cases were treated strictly in the orthodox manner, that is, three tablets were given each day (one three times a day) for five days. The urine was examined before treatment and again after the treatment was completed. Likewise on the sixth day a thick film was examined, and if asexual forms were found the atebrine course was repeated after a lapse of a few days.

The quinine cases were treated in our usual manner. Ten grains of quinine were administered three times a day until the fever had subsided and for at least five days thereafter or for five days after all symptoms, save those due directly to the quinine, had disappeared. Serious cases, such as the various pernicious types, were treated, of course, with a heavier dosage. Thus the quinine treatment required usually a considerably longer hospitalization period, but it seemed only fair to treat these cases exactly as we had always handled them before. Thus only could a reasonably fair comparison be drawn. In this series also the urine was tested before treatment, and both a urine specimen and a thick film were examined after completion of the course of treatment. If asexual forms were found the treatment was continued for five days longer. When sexual forms alone were found in either the atebrine or the quinine cases after the usual course of treatment, plasmochin compound tablets were given, one three times a day, until the blood smears became and remained negative. At least five minutes were devoted to each thick film examination. Upon final discharge the atebrine cases were given 24 special tonic tablets (Aitkins formula plus an extra grain of quinine in each tablet) to take home, recommending that they take one three times a day. The quinine series were given 24 special tonic and 24 quinine tablets, one of each to be taken three times a day.

The patients in both series were chiefly Colombian mestizos and mulattoes, of the laboring class, these numbering 190. Among the remaining were White Americans 3, Spaniards 2, Scotch 1, Venezuelan mestizo 1, and West Indian negroes 3, one each from Jamaica, Martinique and Grenada.

Other conditions which had to be treated in the various cases along with the malaria, some times as primary, but more frequently as secondary ailments, are listed in table 3.

TABLE III
Associated Diseases

Uncinariasis	60
Ascariasis	31
Amebiasis and amebic dysentery	31
Lobar pneumonia	1
Bronchitis	1
Lung abscess	1
Influenza	9
Tuberculosis	1
Syphilis	14
Gonorrhea (ophthalmia and urethritis)	4
Chancroid	1
Inguinal adenitis	1
Obstetrical cases	3
Cystocele and rectocele with prolapse of uterus	1
Cervicitis	1
Mitral regurgitation	2
Cardio-renal case	2
Nephritis	1
Otitis media	1
Axillary abscess	1
Contusion	1
Stab wound	1
Infection of leg	1
Conjunctivitis	2
Dental caries	11
Splenic anemia	1
Psychasthenia	1

To reach conclusions from this study of 200 cases, 12 important features must be given consideration. These are as follows:

- 1 Comparative efficiencies of quinine and atabrine relative to their action on the asexual forms
- 2 Do both drugs act equally well with plasmochin?
- 3 Comparative costs of the drugs
- 4 Does atabrine appear to be more toxic to the human organism than quinine?
- 5 Is atabrine more pleasant to take than quinine?
- 6 Do patients seriously object to the yellowish pigmentation of the skin which is often produced by physiological doses of atabrine?
- 7 Is the slight gastric distress which attends atabrine ingestion more disagreeable than the tinnitus aureum produced by quinine?
- 8 Which cases seem more prone to relapse—those that have been treated by quinine, or the atabrine cases?
- 9 Which drug yields the better results in severe pernicious malaria such as the biliary remittent, the cerebral, the algid or the cardiac types where intramuscular or intravenous therapy only can be applied?
- 10 The effect of both drugs on the kidneys
- 11 The economic aspect, as determined by observing which type of treatment returns patients to their various duties more promptly
- 12 Consideration of the effects of atabrine and quinine on the pregnant uterus

QUININE SERIJS

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Days 1	T #	Qtn ##	Qtn ##	EA #	EA #	EA #	EA #	EA #	EA #	EA #	T ##	EA #	Qtn ##	Qtn ##	Qtn #	T ##	EA (#)	Qtn ##	EA ##	EA ##
2	Neg	Qtn ##	Qtn ##	Neg	Neg	EA #	EA #	EA #	EA #	EA #	T ##	EA #	Qtn #	Qtn #	Neg	T ##	Neg	Qtn #	EA ##	EA ##
3	Neg	Qtn #	Qtn #	Neg	Neg	EA #	Neg	EA #	EA #	EA #	T #	Neg	Qtn #	Qtn #	Neg	T #	Neg	Qtn #	EA #	EA #
4	Neg	Qtn #	Qtn #	Neg	Neg	EA #	Neg	Neg	Neg	EA #	T #	Neg	Qtn #	Qtn #	Neg	T #	Neg	Qtn #	EA #	EA #
5	Neg	Qtn #	Qtn #	Neg	Neg	EA #	Neg	Neg	Neg	EA #	T #	Neg	Qtn #	Qtn #	Neg	T #	Neg	Qtn #	EA #	EA #
6	Neg	Qtn #	Qtn #	Neg	Neg	EA #	Neg	Neg	Neg	EA #	T #	Neg	Qtn #	Qtn #	Neg	T #	Neg	Qtn #	EA #	EA #
7	Dis	Neg	Dis	Dis	Dis	EA #	Neg	Neg	Dis	Neg	Neg	Dis	Neg	Qtn #	Dis	Neg	Neg	Neg	EA #	Neg
8		Neg				EA #	Neg	Neg		EA #	Dis		Neg	Neg		Neg	Neg	Neg	EA #	Neg
9		Neg				EA #	Dis	Neg		EA #	Dis		Neg	Neg		Dis	Dis	Neg	EA #	Dis
10		Neg				EA #	Neg	Neg		Neg			Neg	Neg				Dis	EA #	Dis
11		Dis				Neg				Neg			Dis	Neg				Dis	EA #	Dis
12						Neg				Neg				Neg					EA #	Dis
13						Neg				Neg				Neg					EA #	Dis
14						Dis				Dis				Dis					EA #	Dis

The discussion of these 12 considerations is as follows

1 *Comparative Efficiency of Quinine and Atebrine, Relative to Their Actions on the Asexual Forms* It is true that often the malarial parasites seem to leave the peripheral circulation when the patient is simply put to bed, given good food, rest, ample fluids to prevent dehydration, and alkalization, even though no specific drugs are administered. It is also true that parasites may be found on thick film examination on a given day and be absent on the next even though the patient has not received even the above described attention. It is moreover true that change of climate, of altitude, exposure to cold, to roentgen-ray treatment, or any lowering of the individual's normal resistance may induce deep seated parasites to enter the peripheral circulation. Yet despite these considerations the best test for comparative efficiency seemed to lie in making daily examinations of thick films in sub-groups of unselected cases while under treatment with these drugs. Hence 20 cases were used in each sub-group, the results of which are shown on pages 359 and 360.

As regards the abbreviations in the above tabulation, E A, of course, stands for estivo-autumnal, Qtn, for quartan, and T for tertian, c stands for crescents, EA signifies rings, and EA&c indicates the presence of rings and crescents. The sign \otimes , used as a plus sign, indicates the degree of infection, (\otimes) meaning $\frac{1}{2}$ plus or equivalent to occasional or extremely few. Dis stands for discharge from hospital.

In almost every case at least three daily negatives were obtained before the case was discharged. These may be considered to mean permanently negative. In some of the cases longer series of negatives were required, chiefly because they were suffering from coexisting maladies and we wanted to be certain that such a sign as continued fever for example might not have been augmented in any way by the malaria. In the atebrine sub-group, contrary to our general plan, atebrine was continued without any lapse where ring forms still persisted on the fifth day. It chanced that the atebrine series contained 12 E A, and 8 T, cases, while the quinine cases were represented by 11 E A, 6 Qtn, and 3 T.

In concluding this, the first of the 12 features, we find that the blood films became permanently negative in an average of $4\frac{1}{2}$ days in the atebrine sub-group and in the quinine sub-group not until $5\frac{7}{20}$ days. But consideration must be given to the fact that the atebrine series contained no quartan cases and that may make some difference. Relapses and length of hospitalization will be considered under separate headings.

2 *Do Both Drugs Act Equally Well with Plasmochin?* In our experience no incompatibility appears to exist between plasmochin and either quinine or atebrine, and each of the latter seem to act in perfect accord and therefore equally well with plasmochin.

3 *Comparative Costs of the Drug* We find that delivered to us in Santa Marta, with duty, cost of shipment and all, the cost of quinine per

tablet is 0 0120 pesos, Colombian currency, atebine 0 0425 pesos, plasmochin compound 0 02 pesos, and ampules of the di-hydrochloride of quinine for intravenous or intramuscular use, each of which contains $7\frac{1}{2}$ grains or $\frac{1}{2}$ gram, cost 0 08 pesos each. The American dollar at the present exchange is worth in Colombia approximately 1 75 pesos. Our investigation shows that in the treatment of 100 cases, 1,590 tablets of atebine were used. The cost of these at 0 0425 pesos per tablet amounted to 67 575 pesos. In treating the quinine cases, as we did, giving each patient also 24 tablets to take at home with the special tonic tablets after his discharge, 7,160 tablets were used. At 0 012 pesos per tablet the cost of treating the series of 100 cases rose to 85 96 pesos. In addition to the tablets of quinine, 14 ampoules of the di-hydrochloride were also used for the treatment in certain of the pernicious manifestations. It chanced that in the atebine series none of the cases required intramuscular or intravenous therapy. As our routine included the administration of one tablet of plasmochin compound every night, and as the quinine series required longer hospitalization, 549 plasmochin compound tablets were used in the atebine series against 736 in the quinine group.

4 *Does Atebrine Appear to Be More Toxic to the Human Organism than Quinine?* No real objective signs of any toxicity were noted, and I do not believe that the yellowish pigmentation of the skin enters into this category. Urine examinations before and after treatments will be discussed under a separate heading. None of the cases in either group manifested idiosyncrasies. This was fortunate for when this phenomenon complicates quinine administration it can be not only extremely distressing but also quite alarming. We have as yet seen no such untoward manifestation with atebine.

5 *Is Atebrine More Pleasant to Take Than Quinine?* Even though atebine is bitter nearly all patients agree that it is more pleasant to take than is quinine. To children it can be given in required fractions of tablets while quinine has always to be prescribed either in the form of the comparatively tasteless and far less soluble ethyl carbonate, which is expensive, or must be disguised by syrup or other sweetened adjuvants. For adults, the bitterness of the quinine need cause scarcely any discomfort since sugar coated tablets are found to be quite as soluble as the uncoated ones.

6 *Do Patients Seriously Object to the Yellowish Pigmentation of the Skin Which Is Often Produced by Physiological Doses of Atebrine?* The few really white skinned patients in our series did not object, in the others, chiefly mulattoes and mestizos, it was scarcely noticeable.

7 *Is the Slight Gastric Distress Which Attends Atebrine Ingestion More Disagreeable than the Tinnitus Aureum Produced by Quinine?* In this the opinions of patients who had taken both drugs were equally divided, the more phlegmatic apparently not objecting as much to the tinnitus as to the gastric discomfort when the latter was in evidence. In most cases no gastric symptoms were noted. I do believe that in field work and for blanket treat-

ments, the average patient would be more likely to take the course of 15 atebriane tablets than a course of quinine which would require at least double or triple that number of tablets

8 *Which Cases Are More Prone to Relapse—Those That Have Been Treated by Quinine, or the Atebrine Cases?* In each series 5 cases were known to relapse or become re-infected. In the atebriane series there were 3 tertians and 2 estivo-autumnal cases which, when they were readmitted to the hospital, were found to have tertian parasites. One of the tertian cases was readmitted twice, each time at several months intervals. The quinine relapse group presented 3 estivo-autumnals and 2 tertians one of which, on returning, was found to have estivo-autumnal organisms. Other cases might have relapsed and returned for dispensary treatment only. We would have no record of these.

9 *Which Drug Yields the Better Result in Severe Pernicious Malaria Such as the Biliary Remittent, the Cerebral, the Algid or the Cardiac Types Where Intramuscular or Intravenous Therapy Only Can Be Applied?* We have in our possession ampules of atebriane for intramuscular and intravenous use. It chanced that the atebriane series presented no pernicious case which required extra-oral administration of the specific, and we were determined, when we began this investigation, that we would not select cases. Frankly, I have had such satisfactory results generally with the intramuscular injections of quinine combined with adrenalin, or by giving quinine intravenously, very slowly and cautiously, well diluted in saline (or preferably hypertonic glucose solution), that had I had, for example, in my atebriane series a case either unconscious with cerebral malaria or with such persistent vomiting as to preclude oral administration of the drug, the sort of complication one finds in the biliary remittent type (incidentally the commonest and fortunately the least dangerous of the pernicious forms), I should unhesitatingly have used this form of quinine treatment first, to be followed, when possible, by atebriane by mouth. And this is the type of treatment I now unhesitatingly advise until we learn more about the intravenous and intramuscular administration of atebriane.

10 *Effect of Both Drugs on the Kidneys* Traces, and even larger amounts of albumin, and hyaline and occasional granular or even epithelial casts are signs of the cloudy swelling of the kidneys which, along with all the other parenchymatous organs, are involved in any such febrile condition as malaria. It is not surprising then that our records show substantial improvement in the urinary picture in the majority of specimens examined after the treatment had been completed. This is illustrated in the following tabulation:

	<i>Atebrine</i>	<i>Quinine</i>
Substantial improvement after treatment	49	51
Condition about the same after treatment	9	7
Condition worse after treatment	5	3
Urine picture normal both before and after treatments	36	36
No second specimens obtained	1	3

Some of the cases, of course, as herein before stated, suffered primarily from kidney conditions while in other instances renal degeneration continued to progress because of aggravation from the various contributory diseases mentioned in the foregoing list of secondary ailments

11 *The Economic Aspect by Determining Which Type of Cases Return to Their Various Duties More Promptly* I have stated before that the atebaine course of therapy is generally definitely shorter than the quinine course. Counting the hospital days from the temperature charts would not be absolutely correct because it was necessary frequently to retain patients for treatments of conditions other than malaria. As accurate a way as any to make an estimate from our investigation would be to double the 1,590 atebaine tablets used in the series because of these only 3 were used each day, and determine the ratio between that sum and the amount represented by the 7,160 quinine tablets from which 2,400 should be deducted in that this amount was given to the patients to take home with them. Thus the ratio of the average atebaine hospitalization time to the average hospitalization time for quinine cases is as 3,180 is to 4,760, signifying that atebaine cases are kept in the hospital for treatment only about two-thirds as long as the quinine cases.

12 *Consideration of the Effects of Atebrine and Quinine on the Pregnant Uterus* One case, a young American primipara, was given a complete course of atebaine and plasmochin compound almost at the end of her confinement. It produced absolutely no untoward effect, and influenced in no way whatsoever a quite normal delivery at full term.

Despite the insistence of some of our colleagues that it is the malaria and not the quinine that so often untimely terminates uterine life, we have always been very cautious in administering quinine to our pregnant cases, insisting upon their remaining in the hospital where they can be closely watched, and administering quinine in smaller and more frequent dosages, as for example, 5 grains every 3 or 4 hours, totalling 20 to 25 grains per day. It is certain that malarial cases must be treated despite pregnancy and if quinine is really toxic in these cases, as we believe it is, it is hoped that atebaine will be found to be definitely safer to administer in these conditions.

Dr M. E. Duran of our hospital staff believes that in his experience the quinine seems to reduce the fever more quickly than the atebaine. "At least one day sooner" was the doctor's assurance. A perusal of my series of charts seems to confirm this observation. If this shall be proved to be substantially true then a last recommendation of this paper may be to the effect that after all, quinine had best be given for a day or two before beginning the five day atebaine treatment, including therein the plasmochin compound tablet every night.

Almost a year has transpired since the completion of this report, and our records show that during this time 10 of the atebaine series of 100 cases, and 10 of the quinine series of 100 were re-admitted for malaria. Of the

10 atebrine cases, 6 were originally estivo-autumnal and of these 3 returned with estivo-autumnal and 3 with tertian malaria. Three of these atebrine series were tertian of which 1 returned with tertian, 1 with estivo-autumnal, and 1 returned twice with tertian and once with estivo-autumnal infections. The remaining 1 of the 10 was quartan and our records show that he was readmitted with estivo-autumnal malaria. Now of the 10 cases of the quinine series which returned during this time, 5 were originally estivo-autumnal, 4 were tertian and 1 was quartan. Of the estivo-autumnal infections, 3 returned once with estivo-autumnal, 1 returned twice with estivo-autumnal, and one returned with tertian parasites. Three of the 4 tertian cases returned with tertian parasites and 1 with estivo-autumnal infection. The quartan case presented estivo-autumnal malaria on return.

In concluding, I want to thank Dr L M Drennan for all of his kind cooperation in making this investigation possible, Dr Juan Davila for his able assistance in following up a number of the cases while taking over my service for a short period, Sr A E Gil del Real and his laboratory staff for their excellent service, and cooperation, as well as the nurses who carried out the treatments faithfully and intelligently.

CORONARY ARTERY DISEASE AND ANGINA PECTORIS, THE PRESENT STATUS WITH A REVIEW OF SOME OF THE RECENT LITERATURE

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IN presenting a paper on this subject it seems advisable to begin with an explanation. For although relatively few contributions were made in the century and a half which elapsed between the epochal work of William Heberden¹ in 1768 and that of James B Herrick^{2, 3} in 1912 and 1918, a wealth of material on this theme has appeared in the world's medical literature of the last 20 years. The usefulness of an additional paper on the general subject at this time might, therefore, properly be questioned. At the risk of such criticism and with the realization that much of the material here discussed has already been presented in the collection of splendid articles recently published under the editorship of Robert L. Levy,⁴ the writer nevertheless considers it worthwhile to make available in a single paper a summary of the accumulated information upon a subject of such vital and increasing importance. The attempt perhaps receives further justification from the fact that in recent years the conviction has been growing that the incidence of coronary heart disease the world over has been continually increasing,^{5, 6} and that physicians are among its most frequent victims^{7, 8, 9}

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

Although it has been repeatedly demonstrated that anatomically the two coronary arteries communicate with each other and that either artery can be injected from the other, physiologically this anastomosis must be quite limited, since occlusion of a major coronary branch almost always results in an infarct with rapid necrosis of the cardiac tissue. Furthermore, the coronary system is to a large extent isolated from the general circulation, and except for very slight and inadequate communications with the vasa vasorum of the main vessel and with the circulation of the pericardium and of other mediastinal structures, no important connections exist with extra-cardiac vascular territories.

The venous system of the heart is more variable in structure than the arterial. Most of the cardiac veins open into the coronary sinus, which is situated in the posterior part of the coronary sulcus and ends in the right atrium. A substantial but variable number of cardiac veins drain directly into the right atrium. Recently considerable attention has been directed to the possible importance of the Thebesian veins in the nutrition of the heart under certain pathological conditions. These veins (first described by Adam Christian Thebesius in 1708) are minute channels which

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arise in the muscular wall of the heart and open directly into the cardiac chambers. The majority open into the auricles, a few end in the ventricles. More than 90 per cent of the exits are on the right side of the heart¹⁰. It appears probable that these minute veins, normally a part of the drainage system, may under certain circumstances, when pressure relations are reversed, assume an irrigating function¹¹. Such reversal of pressure gradients can occur when a large branch of a coronary artery is occluded¹⁰. The formation of an infarct may thus be prevented by a reversal of flow in the Thebesian channels. However, since only an insignificant number of these channels open into the left ventricle, little practical benefit to this chamber can be derived from that source. "It is no doubt this peculiar circumstance that makes infarction of the auricles and of the right ventricle so rare and infarction of the left ventricle under like circumstances so common"¹⁰.

The coronary circulatory system is in large part enclosed by the constantly active muscle walls of the heart. Due to this circumstance, the coronary vessels are subjected to constant passive variation in their caliber. This variation in caliber and the aortic pressure constitute the major factors in the determination of the blood flow in the coronary vessels¹⁰. During systole the resistance within the coronary system is obviously greatly increased. However, as has been shown by Wiggers and his associates,¹² even during the phase of maximum systolic contraction, "the intramural pressure never equals the aortic pressure", and consequently "intramural compression is not ordinarily sufficient to arrest coronary flow, but merely tends to retard it". It follows from the foregoing that although the coronary flow during systole is not completely arrested, the diastolic flow normally exceeds the systolic because the resistance is less and because the diastolic phase is normally longer than the systolic.

CORONARY ARTERY DISEASE AND MYOCARDIAL INSUFFICIENCY

It has been pointed out that impairment of the coronary circulation is more apt to affect the left ventricle than the right. Although sooner or later weakness of both ventricles supervenes, it not infrequently happens that symptoms of left ventricular failure are the first and for some time remain the dominant manifestations of coronary artery disease. Briefly, such signs and symptoms are of two categories: (a) those due to congestion of the pulmonary circulation and (b) those due directly to muscle impairment. Symptoms due to pulmonary congestion are (1) dyspnea (without peripheral edema), (2) paroxysmal (often nocturnal) dyspnea, (3) increased pulmonary vascular markings (roentgenographical), (4) increased pulmonary second sound, and (5) diminished vital capacity. The signs due more directly to muscle wall impairment are (1) protodiastolic gallop rhythm and (2) pulsus alternans. Of the causes which produce left ventricular failure the most important are (1) hypertension, (2) aortic

disease, and (3) coronary artery disease¹³ If hypertension and aortic valve defects can be excluded, the development of myocardial insufficiency in which weakness of the left ventricle is the dominant factor, strongly suggests coronary artery disease

CORONARY ARTERY DISEASE AND ANGINA PECTORIS

With the general recognition that coronary insufficiency is the most important cause of angina pectoris, there has been a growing tendency to regard coronary disease and the anginal syndrome as essentially the same condition. This view is not altogether justified. Although coronary sclerosis is found in the vast majority of patients exhibiting the anginal syndrome, there is a substantial number of cases, variously estimated as between 10 and 50 per cent (the former figure is probably more nearly correct), in which the syndrome is due to causes other than disease of the coronary arteries. It is also quite generally known that many patients (probably close to 50 per cent) with extensive coronary artery disease never suffer anginal pain. Coronary artery disease is a pathological entity, but its clinical manifestations are varied. Although it is often attended by characteristic symptoms, in some instances such symptoms may be entirely absent or they may be so obscure that the condition remains unrecognized throughout life. On the other hand, angina pectoris is essentially a clinical syndrome and its diagnosis is based wholly upon the history. Its pathological background varies from complete absence of anatomical changes to the presence of extensive alterations involving the coronary arteries, the heart, its valves, the aorta, the blood, or blood-forming organs.

ANGINA PECTORIS ETIOLOGICAL AND PATHOLOGICAL TYPES

The essential pathological physiology underlying the anginal syndrome is believed to be an anoxemia of the myocardium. This may be brought about in the following manner: (*a*) by an obstruction of the blood channels (coronary artery disease), (*b*) by a deficiency in the quantity or quality of the blood (severe anemia, especially pernicious anemia), and (*c*) by an impairment of the mechanism, or pressure gradients, by means of which the blood is propelled into and through the coronary arteries. As pointed out above, the two most important factors which determine coronary flow are aortic pressure and the variation in intramural resistance resulting from phasic activity of the cardiac muscle. Hence, anything which interferes with adequate systolic and more especially with adequate diastolic pressure or with the length of diastole, will interfere with efficient coronary flow and produce an anoxemia. In this category are included aortic valvular disease (regurgitation or stenosis), and less commonly mitral stenosis, tachycardia, especially the paroxysmal type, and hyperthyroidism. Toxic and functional states have been regarded as possible factors producing coronary

spasm and myocardial anoxemia, but their importance is not universally acknowledged by physiologists¹⁰ The effect of tobacco, alcohol and other drugs and chemicals also remains disputed From a clinical investigation in which the past habits in the use of tobacco and alcohol of 750 consecutive patients with angina were compared with similar habits of 750 patients without angina, White and Sharber¹⁴ arrive at the conclusion that these two agents are without significant effect upon the genesis of angina pectoris The rôle of extracardiac factors should be mentioned for the sake of completeness, but their importance in the causation of angina pectoris is relatively insignificant I refer to aortitis¹⁵ (without coronary involvement), and to diseases of the esophagus and stomach¹⁶

SYMPTOMS OF ANGINA PECTORIS

The characteristic symptom of angina pectoris is the sudden onset of a severe choking or throttling pain which usually originates in the upper or middle sternum, and often radiates to the left arm and hand, sometimes to other parts of the chest, and less frequently to the neck, back, and right arm The pain is agonizing in character and is usually provoked by physical exertion, emotional excitement or by exposure to cold Less frequently an attack may occur while the patient is at rest or may even arouse him from sleep There is usually no apparent disturbance in the heart action The pulse as a rule remains unchanged, although the blood pressure may rise slightly After a few minutes, especially if nitroglycerine or amyl nitrite is administered, the attack subsides Rarely does an acute attack last longer than 15 or 20 minutes, although some slight discomfort may continue for a half hour or longer

DIAGNOSIS OF ANGINA PECTORIS

The diagnosis of angina pectoris is dependent wholly upon the history Although in many instances some cardiovascular disorders may be found, such changes are not characteristic, and in about one-fifth of the cases no abnormalities are observed upon physical, roentgenographic, or electrocardiographic examinations^{5, 17} The diagnostic triad which is usually necessary or sufficient to establish the diagnosis of angina pectoris is (1) the location and character of pain, (2) the presence of a provocative factor (exertion, emotional excitement, or exposure to cold), and (3) the brief and paroxysmal nature of the attack But although the presence of the "anginal syndrome" is established wholly from the history, it is necessary in every instance to determine if possible the underlying pathology by routine diagnostic procedures including electrocardiographic and roentgen-ray examinations

The differential diagnosis usually presents little difficulty Conditions which sometimes have to be considered in such a differential diagnosis are

neurocirculatory asthenia, pericarditis, herpes zoster, tabes dorsalis, mediastinal or bronchial tumor, diaphragmatic hernias, and diseases of the bones, joints, muscles, and bursae of the upper chest

PROGNOSIS OF ANGINA PECTORIS

The prognosis of angina pectoris depends to a considerable extent upon the underlying pathology. As a rule the prognosis is more grave in the presence of serious anatomical changes and more favorable if cardiovascular abnormalities cannot be demonstrated. However, in many instances the patient is able to carry on with occasional attacks over a period of many years even in the presence of obvious organic disease, while in other instances death may occur during an attack, although no serious anatomical changes can be demonstrated even at necropsy. It follows that the prognosis of angina pectoris is very uncertain, for although the outlook is generally grave, a patient may live with occasional attacks for an indefinite period of time, and in some instances the attacks gradually diminish in frequency or even cease altogether.

CORONARY ARTERY DISEASE ETIOLOGICAL AND PATHOLOGICAL TYPES

The etiology of coronary artery disease, like that of generalized arteriosclerosis, is essentially obscure. In the majority of cases the lesion is of the senile atherosclerotic type with no distinct etiological background. It may occur at any age, but it is most often observed in persons past middle life.

The influence of heredity is generally recognized. The "constitutional" factor is especially stressed by Levine^{18, 19}. The "well set, stocky, strong man" with "rounded forearms" appears to be the type most apt to develop coronary sclerosis and angina pectoris.

The sex incidence also appears significant. In women coronary disease seldom occurs except in the presence of hypertension or diabetes²⁰, but despite the slightly higher frequency of hypertension in women, the incidence of coronary disease among them is only about one-fourth that among men^{18, 19, 20}. This latter circumstance to some extent impairs the significance of hypertension as a cause of coronary disease which would be suggested by the relatively frequent association of these two conditions in both sexes.

In a small number of cases, more specific etiological factors may be apparent. Thus coronary disease may be caused or accelerated by the presence of diabetes or gout, also special types of lesions involving the coronary arteries are sometimes encountered in Buerger's disease and in syphilis. The latter in rare instances may produce a diffuse arteritis affecting the larger or the smaller coronary branches^{21, 22}. The usual syphilitic lesion affects the coronary arteries in a limited area at their ostia, generally as an extension of the same process involving the ascending portion of the aorta. Von Glahn²³ noted that the process is more apt to affect those arteries whose

orifices are "situated either at the upper limit of the sinuses of Valsalva or above this level, where the syphilitic process in the aorta usually ceases. The orifices of those arteries arising normally are seldom involved."

In recent years the rôle of disturbed cholesterol metabolism in the etiology of atherosclerosis has received much attention^{24, 25, 26, 27, 28}. The ability to produce the lesion in rabbits by means of cholesterol feeding appears to have been demonstrated beyond question. Hypercholesterolemia, invariably present in the experimental lesion, is also frequently observed in clinical atherosclerosis. However, as pointed out by Anitschkow,²⁵ Menne,²⁸ and others,²⁷ human atherosclerosis appears to be the result of combined etiology ("combination theory" of Anitschkow) including, in addition to the disturbed cholesterol metabolism, such important predisposing factors as mechanical strain, disordered endocrine function, infection, and toxemia. Hence, in the light of present knowledge, it appears that hypercholesterolemia arising from overdosage or from other causes, although of probable importance in conjunction with the aforementioned predisposing factors, cannot be regarded as of exclusive etiological significance.

CORONARY ARTERY DISEASE CLINICAL TYPES

The variation in the clinical manifestations of coronary artery disease is dependent upon three factors: (1) the degree of coronary narrowing, (2) the rapidity with which narrowing or obstruction develops, and (3) the sensitivity of the patient, or the variance of the pain threshold. The first two factors are self-evident. The third is assumed as an explanation for the variation in the degrees of pain which attends sudden coronary occlusion in different individuals, and for the fact that in rare instances no pain at all is experienced. The clinical types thus recognized are:

(A) Cases of coronary sclerosis with gradual narrowing and slowly developing myofibrosis, presenting the following clinical manifestations: (1) paroxysmal attacks of angina pectoris, (2) varying degrees of myocardial insufficiency more especially of the left ventricular type, and (3) varying degrees of heart block, ectopic beats, and less frequently, other disturbances in rhythm. All of these manifestations singly or combined may be observed in any individual case, or no symptoms may be present, and the condition is found at necropsy when death results from some other cause.

(B) Cases of more or less sudden complete occlusion of an important coronary branch, resulting in myocardial infarction and one or more of the following clinical manifestations: (1) sudden death, (2) sudden onset of severe anginal pain which persists for a period of hours or days (status anginosus) with collapse, nausea and vomiting, fever, leukocytosis, increased sedimentation rate, embolic phenomena, pericardial friction rub, and myocardial insufficiency in which weakness of the left ventricle predomi-

nates, (3) sudden attack of acute dyspnea (cardiac "asthma") with no pain but with gradual development of myocardial insufficiency in which at the onset weakness of the left ventricle is apt to predominate, and (4) a somewhat unusual type of "occult" coronary occlusion

In the latter no clinical disturbance occurs at the time of the occlusion, and the patient, unaware that anything serious has happened, continues about his business. In rare instances the infarct heals without ever producing clinical symptoms and remains undiscovered, or is found at necropsy after death from some other unrelated cause. More often, after a period of time, there develop gradually increasing dyspnea and other signs of myocardial insufficiency with left ventricular weakness predominating in the earlier stages.

This type of myocardial insufficiency merits special emphasis as its true nature is often overlooked. It is exemplified by the following observation. A 46 year old salesman with a negative past history and with an available record which definitely excluded syphilis, rheumatic fever and hypertension, more or less suddenly developed dyspnea on moderate exertion. He was nevertheless able to continue his usual occupation for about three months when one night some two weeks before death, he awoke with a severe attack of "asthma." Following this episode he was forced to remain in bed because of marked weakness, continuous shortness of breath, and frequent seizures of intense dyspnea. On several occasions during this illness the systolic blood pressure was found to be between 90 and 110. There was no cardiac pain, and no evidence of valvular disease was noted by the family physician. Only slight edema of the legs appeared a day or two before death. The writer was summoned for the first time one midnight during the final attack of paroxysmal dyspnea. The patient died before an examination could be made. However, the history as related above suggested the diagnosis of "painless" coronary occlusion with myocardial infarction and myocardial insufficiency primarily of the left ventricular type.

At autopsy there were found (1) an "old" recanalized thrombus of the circumflex branch of the left coronary artery with an "old" healed infarct of the posterior wall of the left ventricle, and (2) a "recent" thrombus of the anterior interventricular branch of the left coronary with extensive anemic infarction of the myocardium of the left ventricle and the interventricular septum with mural thrombosis, and acute hemorrhagic and fibrous pericarditis.

It is evident that the "old" occlusion of the circumflex branch was responsible for the early relatively mild symptoms, and that the "recent" occlusion of the anterior descending ramus coincided with the onset of the severe paroxysms of dyspnea which terminated in death ten days later. No pain was associated with either of the two attacks of coronary thrombosis.

DIAGNOSIS OF CORONARY ARTERY DISEASE

From the foregoing account of the clinical manifestations of coronary artery disease it is evident that its diagnosis is suggested by (1) the occurrence of anginal attacks in the absence of serious valvular disease, severe anemia, or any of the other causes of angina pectoris described above, (2) the development of myocardial insufficiency especially of the left ventricular type, in the absence of hypertension, valvular disease, or any other discoverable cause, and (3) the occurrence of a clinically recognizable attack of acute coronary thrombosis. The diagnosis may be further confirmed by the presence of suggestive or characteristic electrocardiographic changes.

DIAGNOSIS OF ACUTE CORONARY OCCLUSION

A typical attack of acute coronary thrombosis is usually readily recognized by the character of the pain and the associated phenomena tabulated below. The pain of acute occlusion, although similar to the pain of angina pectoris, differs from the latter in that it is more prolonged, is apt to be more severe, is not usually related to an antecedent provocative factor, such as exertion, emotion, etc. (in about 40 per cent of the cases coronary thrombosis occurs during sleep²⁰), and is not relieved by nitrites.

The differential diagnosis of angina pectoris and acute coronary occlusion is indicated in the following table.

	Angina Pectoris	Acute Coronary Occlusion
1 Character of pain	Same	Same
2 Location of pain	Upper and middle portion of sternum	Lower part of sternum
3 Provocative factor	Usually present	Usually absent
4 Behavior	Immobile	Restless
5 Duration of pain	Minutes	Hours or days
6 Effect of nitrites	Relief	No relief, may be harmful
7 Nausea and vomiting	Absent	Usually present
8 Dyspnea	Usually absent	Usually present
9 Collapse	Usually absent	Usually present
10 Acceleration of pulse rate	Usually absent	Usually present
11 Blood pressure	Usually slight rise	Usually falls, sometimes initial rise followed by fall
12 Fever and leukocytosis	Absent	Present
13 Sedimentation rate	Normal	Increased
14 Electrocardiographic changes	May be absent	Usually present and characteristic
15 Pulmonary edema	Absent	May be present
16 Pericardial friction rub	Absent	May be present
17 Embolic phenomena	Absent	May be present

CORONARY ARTERY DISEASE ELECTROCARDIOGRAPHIC CHANGES

In acute coronary occlusion the electrocardiographic changes are almost always sufficiently characteristic to be practically diagnostic, both as to the presence of the lesion and as to its location. This is especially true if serial tracings are available. Anterior infarction, usually located at the apex of

the left ventricle, is due to thrombosis in the left coronary artery. In the electrocardiogram it is indicated by (1) a shift of the RS-T segment upward in Lead I and downward in Lead III, (2) inversion of the T-wave in Lead I, and increased height of the T-wave in Lead III. There is usually a diminution of the amplitude of the QRS in Lead I, and sometimes also in Leads II and III. A well-marked Q-wave sometimes appears in Lead I, and a large S-wave not present before may appear in Lead III.

Posterior infarction is usually located at the base of the left ventricle posteriorly and often involves the adjacent part of the interventricular septum. It is due to a thrombosis in the right coronary artery and is indicated in the electrocardiogram by changes essentially the reverse of those produced by an anterior infarct: (1) a shift in the RS-T segment upward in Lead III and downward in Lead I, (2) the T-wave is inverted in Lead III and remains upright in Lead I. A wide and deep Q-wave appears in Lead III and usually also in Lead II.

In either type of infarction in the course of time the RS-T segment tends to return to the isoelectric level and at the same time the inverted T-wave tends to increase in depth and width. "Just before the disappearance of the shift the RS-T segment may present an upward convexity followed by a more or less sharply inverted T-wave. It is essentially a diphasic T-wave directed first upwardly, then downwardly."³⁰ This is the so-called coronary T-wave of Pardee.³¹ "In Leads I or II it is almost pathognomonic of coronary occlusion. In Lead III, unless accompanied by changes in other leads, it is not so significant."³⁰

In the chest lead (IV) with the exploring electrode over the apex of the heart, an anterior infarct causes a disappearance of the Q-wave (normally deep and wide) and an upright or a diphasic T-wave (normally more or less sharply inverted). * "Because of the distance of the posterior surface of the heart from the chest wall, posterior infarcts are not readily revealed by this means."³⁰

Coronary sclerosis without thrombosis is apt to produce irregular electrocardiographic changes involving any or all of the waves and complexes depending on the extent of cardiac muscle damage which resulted from the arterial disease. Such changes, however, are not characteristic or diagnostic, since myocardial damage from any other cause may produce similar alterations. Sometimes an entirely normal tracing is obtained in the presence of extensively diseased coronary arteries. Normal electrocardiograms have been obtained in some instances a few days and a few hours before the occurrence of an acute occlusion. Sometimes even after the occlusion,

* Since this paper was submitted for publication, the method for taking chest leads has been changed at the recommendation of the committees of the American Heart Association and of the Cardiac Society of Great Britain and Ireland, with the result that relative positivity of the chest electrode causes an upright deflection. The tracing obtained by the new method is essentially a mirror image of the old Lead IV. (Standardization of precordial leads, Jr. Am. Med. Assoc., 1938, cx, 395, Standardization of precordial leads, Supplementary report, *ibid*, 1938, cx, 681.)

a tracing is obtained which presents little or no deviation from the normal, although several hours later typical electrocardiographic changes develop

PRELIMINARY OF PREMONITORY PAIN IN CORONARY THROMBOSIS

Recently attention has been called to the occurrence of substernal or epigastric pain preceding by hours or days the onset of acute coronary occlusion. This differs from the typical anginal pain, from which the patient may or may not have suffered in the past, in that it is usually milder, is not related to effort, is more prolonged, and does not significantly respond to nitrites. It is also distinguishable from the pain of actual occlusion in that it is not accompanied by any of the objective findings usually present in the latter such as fever, leukocytosis, accelerated sedimentation rate, or characteristic electrocardiographic changes.

Feil³² noted such preliminary pain in 15 cases of acute coronary occlusion. Sampson and Eliaser³³ reported this symptom in 29 cases. These figures represent about half the total number of cases of coronary thrombosis studied by those authors over a given period.

It is often the experience of the student confronted with a newly-described sign or symptom to find, upon a search of the literature, similar observations already recorded. Sampson and Eliaser quote Herrick,² who as early as 1912 mentions in one of his case histories a premonitory attack of pain of unusual nature arising three days prior to the occlusion. They also note that Conner and Holt³⁴ and Parkinson and Bedford³⁵ "describe the occurrence of transitory pains in the chest of a nature different from previous anginal attacks." Levine¹⁸ in his recent book states that "on close questioning many (patients) will confess that during the preceding day or two they had not felt quite well, and may have had more or less milder discomfort in the chest." And earlier (1929) in his monograph on coronary thrombosis Levine¹⁹ records two case histories with premonitory pain. In one (case 39) the "patient who was always strong, vigorous and active" stated that "on the day before the severe attack there were a few premonitory anginal spells." In the other (case 120) "the interesting features were the premonitory symptoms for several days when the attacks that previously lasted a few minutes began to last a few hours." Willius³⁶ reported a patient with coronary sclerosis and anginal attacks of five years' duration who, on the day preceding a typical attack of coronary thrombosis had suffered "an oppressive retrosternal recurrent pain which was relieved by acetylsalicylic acid." This pain occurred while the patient was motoring and was apparently different from his accustomed anginal attacks. There were also "no abnormal findings revealed by examination including electrocardiographic study." It was Willius' opinion that "the mild recurrent retrosternal pain which occurred the day before the attack of complete coronary obstruction represented the period when the thrombus was form-

ing These symptoms are probably dependent on the rate at which the artery becomes occluded "

The significance of this pain is not altogether established Both Willius and Feil suggest that a gradually forming thrombus in a stenosed coronary artery appears to be the most probable cause of the premonitory pain If this explanation is correct the development of such pain assumes important diagnostic and prognostic significance Sampson and Eliaser³³ discuss the possible importance of enforcing bed rest immediately upon the appearance of premonitory pain, but they are unable to reach any conclusion as to the value of such enforced rest in the prevention of the final occlusion

THE PERICARDIAL FRICTION RUB

The development of an audible pericardial friction rub is dependent upon (1) the location of the infarct in relation to the anterior chest wall and (2) the extension of the infarct outward so as to involve the pericardium Although anterior infarction is admittedly more frequent than posterior, the preponderance of the anterior lesion is probably not so great as was formerly believed In 46 autopsied cases Levine¹⁹ found the lesion within the distribution of the anterior descending branch of the left coronary in 39 instances, or in about 85 per cent However, in a large series of cases Willius³⁷ found anterior and posterior infarction in the relation of 56.3 per cent and 43.6 per cent respectively, and Master, Jaffe and Dack³⁸ in a clinical study of 243 patients found anterior and posterior lesions with equal frequency It is clear, therefore, that in a large number of cases the infarct is located posteriorly and the involvement of the pericardium in this location is less likely to produce an audible friction rub Furthermore, as was pointed out by Bedford³⁹ a myocardial infarct quite often extends inward and involves the endocardium, but, due to the relatively more abundant (extracardiac) collateral circulation of the epicardial surface, the infarct less frequently extends outward far enough to involve the pericardium It follows that the pericardial friction rub, although a valuable diagnostic sign and one which should always be sought for closely, is not so common as might be inferred from the frequent reference to it in the literature Levine¹⁹ in his series of cases referred to above, notwithstanding the great predominance of anterior lesions, noted friction rubs in only 13.8 per cent When present it is usually heard best at or near the apex, and generally first appears in from one to several days after the onset of the attack

EMBOLIC MANIFESTATIONS

In consequence of the frequency with which the ventricular endocardium is involved in infarction, mural thrombosis is very common In a recent review of the subject Blumer⁴⁰ estimates that mural thrombosis over the infarcted area occurs in about 50 per cent of the cases In the 45 autopsied

cases of Levine's series¹⁹ mural thrombi were found in 36 (80 per cent) Wolff and White,⁴¹ reporting on 23 autopsied cases, state that "mural thrombosis almost always occurs over the infarcted area" However, embolic lesions recognizable clinically or pathologically are much less frequent In the total of 145 cases reported by Levine embolic phenomena were observed (clinically or pathologically) in only 22 (15 per cent) It is apparent that fortunately in many instances mural thrombi organize without producing clinically important embolic accidents When they so organize, they often serve to strengthen a weakened, thinned-out ventricular scar

Since the left ventricle is more often the seat of infarction than the right, mural thrombosis occurs more frequently in the left ventricle, and emboli are more common in the systemic than in the pulmonary circulation However, due to the relatively frequent involvement of the interventricular septum, thrombi within the right ventricle are not rare, and when present serve as a source of pulmonary embolism Occasionally pulmonary infarction may also result from a paradoxical embolus in the presence of a patent foramen ovale, or it may arise from thrombi formed in the right auricular appendage as a result of auricular distention or auricular fibrillation* In a series of 81 autopsied cases collected from the literature (including 35 of his own) Blumer⁴⁰ found the site of embolism to be distributed as follows: lungs 35, brain 23, kidney 6, spleen 2, extremity 8, periphery 6, and aorta one Thus in this series the proportion of systemic to pulmonary embolism was 46 to 35

FEVER AND LEUKOCYTOSIS

Fever and leukocytosis occur in nearly all cases of acute coronary occlusion They usually develop within 12 hours after the accident and gradually disappear in several days, sometimes they may persist for two weeks or longer In exceptional cases fever and leukocytosis may never develop, or either may develop without the other

SEDIMENTATION RATE

The erythrocyte sedimentation rate begins to rise after 24 to 48 hours and continues to increase for several days It remains elevated for two to four weeks or longer, and with the healing of the infarct it gradually falls to normal In 29 cases studied by Shookhoff, Douglas, and Rabinowitz⁴² the sedimentation rate was abnormally rapid in all In two of these cases the temperature and leukocytosis remained normal throughout the illness

The sedimentation rate is probably the most reliable index of the activity within the infarcted area including the mural thrombus It is of both

*In some instances of coronary occlusion pulmonary embolization results from thrombi originating in the systemic veins due to slowing of the general circulation I have also observed recently an instance of acute coronary occlusion in which on the eighth day after the onset of attack, while the patient appeared to be doing well, death occurred suddenly from massive pulmonary infarction which resulted not from an embolus but from a thrombosis of the pulmonary artery

diagnostic and prognostic importance. In the presence of cardiac pain the failure of the sedimentation rate to rise after several days is evidence against the occurrence of infarction. In known coronary thrombosis a constantly increasing sedimentation rate is an unfavorable prognostic sign, while a gradual decrease is of favorable import.⁴³ The maintenance of a high sedimentation rate is an indication for continued bed rest.

DISTURBANCES IN THE CARDIAC MECHANISM IN CORONARY THROMBOSIS

Cardiac irregularities are common. These include premature beats (auricular and ventricular), auricular fibrillation and (less commonly) flutter, heart block (varying degrees), and paroxysmal tachycardia (auricular and ventricular). These irregularities in rhythm are usually transient and as a rule require no special treatment. The pulse rate is usually rapid, although occasionally the rate may be slow even in the absence of heart block. Gallop rhythm is common and occasionally pulsus alternans is present. The last two disturbances are probably the direct result of weakness of the left ventricle.

CEREBRAL MANIFESTATIONS IN CORONARY THROMBOSIS

Occasionally an attack of coronary thrombosis is ushered in with cerebral symptoms, including convulsions, coma, restlessness, and confusion. They may also develop at any time during the course of the illness. Cerebral anoxemia from heart block or myocardial insufficiency, cerebral emboli, and extreme collapse,^{19, 44} have been suggested as possible causes of these manifestations.

PITFALLS IN DIAGNOSIS

Despite the general appreciation of the various manifestations of coronary thrombosis, there are many clinical conditions with which acute coronary occlusion is not infrequently confused and which need to be borne in mind in a consideration of the differential diagnosis. Among the more important are the following: paroxysmal tachycardia, cardiac neurosis, neurocirculatory asthenia, pericarditis, syphilitic aortitis, rupture of aortic valve, dissecting aneurysm, rupture of aorta (into pericardial sac), pleurisy, pneumonia, massive collapse, acute pneumothorax, spontaneous interstitial emphysema of lungs, pulmonary embolism, herpes zoster, arthritis of costochondral articulations, arthritis of shoulder joint, spondylitis of cervical and upper dorsal spine, tabes with gastric crises, and acute abdominal conditions including perforating peptic ulcer, acute gastritis, acute pancreatitis, gallstones and diaphragmatic hernia.^{45, 46}

Although in most cases the foregoing conditions can be readily distinguished from acute coronary occlusion, there are instances in which a differential diagnosis is extremely difficult, and several days' observation may be required for its establishment.

CORONARY THROMBOSIS, GLYCOSURIA, AND DIABETES

It has been pointed out that coronary disease is common in diabetes. However, it should be emphasized that transient glycosuria is not infrequently observed during the course of acute coronary occlusion and the diagnosis of diabetes must not be made without additional evidence.⁴⁵

PROGNOSIS OF CORONARY THROMBOSIS

It is now generally appreciated that a more cheerful attitude regarding the prognosis of coronary thrombosis is justified.^{37, 38} Under favorable circumstances, when the condition is promptly recognized, the average immediate mortality (within the first six weeks) is probably not over 20 to 25 per cent. Recovery with resumption of normal activity for a period of years is not infrequent. White⁴⁷ recently reported an instance of survival for 25 years although four attacks of myocardial infarction occurred between the ages of 48 and 63 years. The patient finally died of congestive failure at the age of seventy-three. In general a favorable prognosis is indicated by (1) the relative youthfulness of the patient, (2) the absence of a history of previous attacks, and (3) typical and characteristic electrocardiographic changes. Atypical electrocardiographic changes might result from multiple infarctions or from antecedent myocardial damage and therefore indicate an unfavorable prognosis. Very low amplitude of the complexes in all the leads is an unfavorable sign. Marked myocardial insufficiency with evidence of failure of both ventricles is a grave prognostic omen. The prevailing impression that a posterior infarction carries a more favorable prognosis than an anterior lesion is called into question by some recently published statistics.^{38, 48} It seems probable that the difference, if any, is very slight.

TREATMENT

Except in cases of syphilitic origin, the treatment of coronary disease is largely symptomatic. The therapeutic indications are thus dependent upon the prevailing manifestations, of which the most important are (1) angina pectoris, (2) acute coronary thrombosis, and (3) myocardial insufficiency.

Treatment of Angina Pectoris It is generally agreed that the acute attack of anginal pain is most readily relieved by the prompt removal of the provocative factor (cessation of physical effort, etc.) and by the use of *nitrites*. Nitroglycerine in small doses ($\frac{1}{250}$ to $\frac{1}{150}$ grain) is generally preferred. When chewed and swallowed, its action begins within one or two minutes and continues for a half hour or longer. If necessary this dose may be repeated at intervals of 15 to 30 minutes for several hours. To assure success the preparation must be fresh and quickly soluble. A supply from a recently opened container should be procured at least every two months. When nitrites are not available, or sometimes in addition to

nitrites, *alcohol* may prove useful⁴⁹ It may be administered in the form of whiskey or brandy in doses of one to two ounces

During the intervals between attacks the patient's mode of life is so regulated as to avoid undue physical and emotional strain At the onset of the illness it is often helpful to institute bed rest for a week or 10 days However, after an initial rest period, in order to maintain the patient's morale, it is important to encourage the continuation of the accustomed occupation provided that occupation does not involve undue physical or emotional strain Overeating should be strictly avoided at all times and if the patient is well nourished a slight loss of weight is often beneficial

The presence of abnormalities such as obesity, hypertension, and focal infection calls for appropriate measures Likewise special therapy is required in the presence of more specific etiological factors such as syphilis, diabetes, pernicious anemia, paroxysmal tachycardia, aortic valvular disease, and hyperthyroidism Syphilis and diabetes should be treated with particular care In the latter insulin is employed very cautiously, as it is important to avoid sudden wide fluctuations in blood sugar levels In the former the bismuth preparations and iodides are preferable to the arsenicals, at least for the first three or four months of treatment

Of the various drugs employed during the intervals between attacks some are of established benefit, others appear to be of questionable value *Nitroglycerine* in small doses ($\frac{1}{400}$ to $\frac{1}{200}$ grain) taken four or five minutes before some necessary effort may serve to prevent an attack In severe cases where attacks occur at frequent intervals upon slight exertion or even at rest, nitroglycerine ($\frac{1}{500}$ grain) taken at hourly intervals throughout the day may prove useful⁵⁰ *Erythrol tetranitrate*, because of its slower and more prolonged action, is preferable to nitroglycerine for the purpose of preventing nocturnal attacks It is given at bedtime in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain

Although a difference of opinion exists concerning the efficacy of the *xanthine derivatives* in coronary disease and angina pectoris,^{50, 51, 52, 53} the weight of clinical evidence distinctly favors their continued employment In a recent study of the comparative value of the various preparations Brown and Riseman⁵³ found theobromine with sodium acetate ($7\frac{1}{2}$ grains three times daily) and theophylline with sodium acetate ($2\frac{1}{2}$ grains three times daily) the most effective Theophylline, aminophylline, and theobromine calcium salicylate (theocalcine) were found to be relatively less effective Occasionally, however, theobromine calcium salicylate proves effective when the patient fails to respond to any of the other preparations If necessary the administration of a suitable xanthine preparation may be continued with or without brief interruptions over long periods of time Untoward effects are very rarely observed

Recently Riseman and Brown⁵⁰ found *quinidine sulfate* "of distinct value for patients who have cardiac pain while at rest or when in bed"

This drug (in doses of 5 or 6 grains three times daily) is recommended for patients who fail to respond to the nitrites and the xanthine derivatives

For the purpose of inducing sleep and lessening restlessness, in this, as in any other serious illness, the *barbiturates* are valuable. However, no specific effects upon anginal pain can be claimed for them. There appears to be no rational basis for the employment of such compounds as "theominal" (theobromine with phenobarbital) and "theamin with amytal." The indications for each of the ingredients contained in such compounds are quite distinct, theobromine is most beneficial when continued over long periods of time, whereas barbitol should be used only in single doses at rare intervals. Recently considerable evidence has been presented tending to prove that all the barbitals possess toxic side actions upon living tissues,⁵⁴ and their prolonged use should be discouraged.

Treatment of Acute Coronary Thrombosis It is generally agreed that in the acute stage the two most important measures are *rest* and the administration of *morphine*. Morphine is especially valuable for it not only lessens the exhausting, agonizing pain and the extreme restlessness, but it also, in some indirect way, favorably influences the function of the left ventricle and diminishes the tendency to pulmonary edema and cardiac asthma. To accomplish these results large doses may be required, often as much as a grain (in divided doses) in a few hours.

Rest should be prolonged. A period of six to eight weeks in bed is generally regarded as a minimum requirement, for this is the average length of time necessary for the healing of the infarct. At the end of such period of bed rest, if the progress is favorable, adequate healing is indicated by (1) the maintenance of a normal temperature, (2) the absence of leukocytosis, (3) the return of the sedimentation rate to normal levels, (4) the absence of pain, and (5) the absence of all signs of myocardial insufficiency. Under such circumstances gradual resumption of activity is permitted.

A highly restricted *diet* is advocated by Master, Jaffe and Dack^{38, 55}. Only small quantities of milk, orange juice and glucose are allowed during the first week, and then, if improvement takes place, the diet is increased to 800 calories per day, at which level it is maintained during the entire period of convalescence. Although this regime may be helpful in the excessively nourished individuals, it does not appear advisable to enforce such drastic undernutrition routinely in all cases. However, overfeeding must always be avoided, and moderate food restriction is desirable in most instances.

During the early course when shock and vomiting prevail, it may become necessary to withhold food completely. At this stage, provided there is no engorgement of the lungs and the systemic veins, the intravenous administration of *glucose* in hypertonic solutions is undoubtedly of value. It is also possible that this procedure may tend to increase the coronary flow and thus exert a more direct beneficial effect upon the nutrition of the heart.⁵⁶ After vomiting ceases, glucose in liberal amounts is given orally. The

caloric value of the glucose thus administered is taken into consideration in connection with the total daily caloric allowance

Oxygen in concentrations of 50 to 60 per cent is advocated by Barach and Levy⁵⁷ The chief indications for its use are (1) cyanosis, (2) marked dyspnea, and (3) pain not relieved by morphine Although a valuable remedy its administration is sometimes difficult because of the discomfort which often attends the use of either the tent or the nasal catheter If those difficulties can be successfully overcome it is desirable, on the average, to maintain its use for about five days, after which, if improvement is noted, the oxygen is discontinued It is important to lower the concentration of the gas gradually before it is completely withdrawn

Aminophylline both by the oral and the intravenous route is widely employed Although, as already stated, the weight of clinical evidence favors the continued use of this (or a similar) preparation as a coronary dilator in angina pectoris, the value of aminophylline in acute coronary thrombosis is open to question Recent studies seem to indicate that this drug does not significantly improve the collateral blood supply to an ischemic area, and that at least in experimental animals, daily injections of fairly large doses fail to exert any influence that can be considered favorable on the course of the infarction^{58, 59}

The position of *digitalis* in the therapy of acute coronary thrombosis is controversial^{19, 38, 55, 60, 61} The majority of experimental studies⁶² indicates that digitalis causes a slight constriction of the coronary vessels and consequently retards the coronary flow However, in the presence of congestive failure it is probable that the improvement in the cardiac function which follows the use of digitalis more than compensates the constrictive effect of the drug upon the coronary vessels Fishberg, Hitzig and King⁶³ in a clinical study of 59 patients with recent myocardial infarction point out that in this condition two distinct mechanisms participate in the derangement of the circulation (a) shock or peripheral circulatory failure which tends to lower the pressure in the systemic veins, and (b) heart failure which tends to cause engorgement of the lungs and to raise the systemic venous pressure The former mechanism is more apt to prevail at the onset of the attack, congestive failure more often develops some days or weeks later The extent of the infarction and the condition of the myocardium prior to the onset of the occlusion probably are additional determining factors of the type of circulatory derangement more apt to predominate Fishberg and his associates thus suggest that the employment of digitalis in myocardial infarction may properly be determined by the prevailing type of circulatory failure In the presence of shock associated with low venous pressure there is no indication for the use of this drug, its administration under such circumstances might indeed be harmful On the other hand in the presence of congestive failure, the cautious use of digitalis is probably helpful

The *nitrites*, so useful in angina pectoris, appear to be of no value in acute coronary occlusion Furthermore, there is suggestive evidence that

the use of these drugs in acute coronary occlusion tends to increase the size of the infarct and may thus be distinctly harmful^{88, 64, 65, 66}

The place of *epinephrine* in the therapy of coronary disease appears paradoxical. Levine, Ernstene and Jacobson⁶⁷ have shown that in patients subject to anginal pain an attack can be induced by means of epinephrine. Experimentally, by intravenous or intramuscular injections of epinephrine, electrocardiographic changes have been produced closely simulating those encountered in angina pectoris and in coronary occlusion^{68, 69}. In view of these facts the drug can hardly be regarded suitable for use in acute coronary occlusion. Nevertheless, Levine¹⁸ has used it frequently for the treatment of heart block complicating coronary occlusion. In several instances he has "given 0.3 to 0.5 c.c. of adrenalin every two hours for 48 hours to patients who had this condition and thereby prevented the pauses of the heart that were otherwise occurring, finally observing that the tendency to syncope had disappeared". The writer's experience with epinephrine in coronary disease has been unfavorable, and in his opinion the use of this drug in myocardial infarction should be reserved for such emergencies as extreme shock or cardiac standstill.

Quinidine has been found useful in the treatment of paroxysmal ventricular tachycardia⁷⁰. Although, like the other cardiac arrhythmias in coronary thrombosis, this arrhythmia in most instances is transient and tends to disappear spontaneously after a few hours, occasionally it may persist and present an important therapeutic problem. Quinidine appears to be the only drug that can control it. The dose is variable. In some instances the arrhythmia is abolished by a single dose of 5 grains, in others much larger amounts of the drug may be required.

Treatment of Myocardial Insufficiency With the exception of the especial care concerning the use of digitalis, which has already been discussed, the management of myocardial insufficiency of coronary origin does not differ in any essential respect from the treatment of congestive failure due to any other cause. A full discussion of this phase of the subject is deemed beyond the scope of this paper. However, it may not be out of place again to call attention to the value of digitalis in the treatment of left ventricular failure before there is failure of the right ventricle. This stage is characterized by dyspnea without peripheral edema. The dyspnea may be more or less continuous, or it may appear in severe paroxysms (cardiac "asthma"), often at night. For the acute attack morphine is the most effective agent, in plethoric individuals venesection is also helpful. Intravenous administration of aminophylline is widely advocated, "but although that procedure is of undoubted value in Cheyne-Stokes breathing, its usefulness in acute paroxysmal dyspnea is not equally apparent".

After the acute attack is controlled, the continued use of digitalis is believed to be the most effective means of restoring the function of the left ventricle and preventing acute paroxysms of dyspnea. The best results are obtained from slow but complete digitalization followed by a daily

maintenance dose of approximately $1\frac{1}{2}$ grains of the powdered leaves. Although this use of digitalis has already been stressed by many authors¹³ the writer is convinced that the importance of this therapy is not yet generally appreciated and that its renewed emphasis at this time is justified.

SURGICAL MEASURES

In closing it is desired to call attention to the recent progress in the surgical treatment of angina pectoris and coronary disease. Generally speaking such therapy is as yet reserved for desperate cases in which relief cannot be obtained from medical treatment. Of the various surgical procedures, the one whose usefulness is definitely established and which may be said to have passed the experimental stage is the paravertebral alcohol injection of the four or five upper dorsal sympathetic ganglia^{71, 72, 73}. The procedure is reasonably safe and is effective in a very high percentage of cases. If the pain is referred to one side only, unilateral destruction of the ganglia on that side is generally sufficient to control it. If the pain is referred to both sides, or if it is felt just under the sternum, bilateral injection is required. For a description of the method of performing these injections the reader is referred to the very lucid and splendidly illustrated article by James C. White⁷¹.

Total thyroidectomy for relief of cardiac pain^{74, 75, 76, 77} and the development of a new blood supply to the heart by grafting tissues (pectoral muscles or omentum) onto the myocardium^{78, 79, 80, 81, 82} are still in the experimental stage. The latter method is particularly promising. It differs from all the other modes of treatment in that it is an attempt actually to reverse the pathological process by restoring the lost blood supply to the heart muscle. Up to the present time (July, 1937) Beck⁸³ has performed this operation upon 25 patients, "in the first 14 cases the mortality was 50 per cent, and the last nine cases have been carried through without a fatality." Beck considers the results as very favorable. "All the patients have been improved, the improvement consists of reduction of pain and increased toleration for exercise. Three patients have been completely relieved of pain and consider themselves cured."⁸³

REFERENCES

1. HEBERDEN, W. Some account of a disorder of the breast, *Med Trans Royal College of Physicians, London*, 1772, 11, 59-67. (The original mention of angina pectoris was made by Heberden in a lecture before the Royal College of Physicians in London, July, 1768.) Cited by White⁴⁹.
2. HERRICK, J. B. Clinical features of sudden obstruction of the coronary arteries, *Jr Am Med. Assoc*, 1912, 11x, 2015-2020.
3. HERRICK, J. B. Thrombosis of the coronary arteries, *Jr Am Med Assoc*, 1919, 1xxii, 387-390.

- 4 LEVY, R L Diseases of the coronary arteries and cardiac pain, 1936, Macmillan Company, New York
- 5 WHITE, P D The diagnosis and medical treatment of angina pectoris, *ANN INT MED*, 1933, vii, 218-228
- 6 DENNY, F P Increase in coronary disease and its cause, *New England Jr Med*, 1936, ccxiv, 769-773
- 7 SMITH, H L Incidence of coronary sclerosis among physicians as compared with members of other occupations, *Jr Am Med Assoc*, 1937, cviii, 1327-1329
- 8 EDITORIAL Obituaries of physicians published in 1936, *Jr Am Med Assoc*, 1937, cviii, 1542-1543
- 9 BECK, C S, and FEIL, H The consideration of the artificial development of collateral coronary circulation by surgical means, *Modern Concepts Cardiovascular Disease*, 1937, vi, No 6
- 10 KATZ, L N The clinical importance of the various factors determining coronary blood flow, *Modern Concepts Cardiovascular Disease*, 1937, vi, No 1
- 11 WEARN, J T The rôle of the Thebesian vessels in the circulation of the heart, *Jr Exper Med*, 1928, xlvii, 293-316
- 12 WIGGERS, C J The physiology of the coronary circulation, *In* LEVY, R L, Editor Diseases of the coronary arteries and cardiac pain, 1936, Macmillan Company, New York, 57-108
- 13 WHITE, P D Weakness and failure of the left ventricle without failure of the right ventricle Clinical recognition, *Jr Am Med Assoc*, 1933, c, 1993-1998
- 14 WHITE, P D, and SHARBER, T Tobacco, alcohol and angina pectoris, *Jr Am Med Assoc*, 1934, cii, 655-657
- 15 ALLBUTT, T C Diseases of the arteries, including angina pectoris, 1915, Macmillan Company, London, ii, part 2
- 16 JACKSON, D E, and JACKSON, H L Experimental and clinical observations regarding angina pectoris and some related symptoms, *Jr Lab and Clin Med*, 1936, xxi, 993-1006
- 17 RISEMAN, J E F, and BROWN, M G An analysis of the diagnostic criteria of angina pectoris A critical study of 100 proved cases, *Am Heart Jr*, 1937, xiv, 331-351
- 18 LEVINE, S A Clinical heart disease, 1936, W B Saunders Company, Philadelphia and London
- 19 LEVINE, S A Coronary thrombosis Its various clinical features, *Medicine*, 1929, viii, 245-418
- 20 LEVY, H, and BOAS, E P Coronary artery disease in women, *Jr Am Med Assoc*, 1936, cvii, 97-102
- 21 MAHER, C C Microscopic pathology of cardiac syphilis, *Am Heart Jr*, 1930, vi, 37-41
- 22 WARTHIN, A S The role of syphilis in the etiology of angina pectoris, coronary arteriosclerosis and thrombosis, and of sudden cardiac death, *Am Heart Jr*, 1930, vi, 163-170
- 23 VON GLAHN, W C The pathology of the coronary arteries, *In* LEVY, R L, Editor Diseases of the coronary arteries and cardiac pain, 1936, Macmillan Company, New York, 129-146
- 24 LEARY, T Atherosclerosis, the important form of arteriosclerosis, a metabolic disease, *Jr Am Med Assoc*, 1935, cv, 475-481
- 25 ANITSCHKOW, N Experimental arteriosclerosis in animals, *In* COWDRY, E V, Editor Arteriosclerosis, a survey of the problem, 1933, Macmillan Company, New York, 271-322
- 26 ANITSCHKOW, N, and CHALATOW, S Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse, *Centralbl f allg Path u path Anat*, 1913, xxiv, 1-9
- 27 KRAFKA, J, JR The mechanical factors in arteriosclerosis, *Arch Path*, 1937, xliii, 1-19

- 28 MENNE, F R, BEEMAN, J A P, and LABBY, D H Cholesterol-induced arteriosclerosis in rabbits, with variations due to altered status of thyroid, *Arch Path*, 1937, **xxiv**, 612-625
- 29 MASTER, A M, DACK, S, and JAFFE, H L Factors and events associated with onset of coronary artery thrombosis, *Jt Am Med Assoc*, 1937, **ci**, 546-549
- 30 ASHMAN, R, and HULL, E Essentials of electrocardiography, 1937, Macmillan Company, New York.
- 31 PARDEE, H E B An electrocardiographic sign of coronary artery obstruction, *Arch Int Med*, 1920, **xxvi**, 244-257
- 32 FEIL, H Preliminary pain in coronary thrombosis, *Am Jr Med Sci*, 1937, **cxciii**, 42-48
- 33 SAMPSON, J J, and ELIASER, M, JR The diagnosis of impending acute coronary artery occlusion, *Am Heart Jr*, 1937, **xiii**, 675-686
- 34 CONNER, L A, and HOLT, E The subsequent course and prognosis in coronary thrombosis, *Am Heart Jr*, 1930, **v**, 705-719
- 35 PARKINSON, J, and BEDFORD, D E Cardiac infarction and coronary thrombosis, *Lancet*, 1928, **i**, 4-11
- 36 WILLIUS, F A Symptoms attending formation of a thrombus preceding complete coronary obstruction, *Proc Staff Meeting Mayo Clinic*, 1936, **xi**, 414-416
- 37 WILLIUS, F A Life expectancy in coronary thrombosis, *Jr Am Med Assoc*, 1936, **cvi**, 1890-1894
- 38 MASTER, A M, JAFFE, H L, and DACK, S The treatment and the immediate prognosis of coronary artery thrombosis (267 attacks), *Am Heart Jr*, 1936, **xii**, 549-562
- 39 BEDFORD, D E Coronary thrombosis, *The Practitioner*, 1933, **cxxx**, 670-683
- 40 BLUMER, G The importance of embolism as a complication of cardiac infarction, *ANN INT MED*, 1937, **xi**, 499-504
- 41 WOLFF, L, and WHITE, P D Acute coronary occlusion, 23 autopsied cases, *Boston Med and Surg Jr*, 1926, **cxcv**, 13-25
- 42 SHOOKHOFF, C, DOUGLAS, A H, and RABINOWITZ, M A Sedimentation time in acute cardiac infarction, *ANN INT MED*, 1936, **ix**, 1101-1105
- 43 CHRISTENSEN, S Remarks on sedimentation reaction in coronary thrombosis, *Ugesk f Laeger, Copenhagen*, 1936, **xcviii**, 221-224, *Abstract Jr Am Med Assoc*, 1936, **cvi**, 2036
- 44 KJAERGAARD, H Cerebral symptoms in acute myocardial infarction, *Acta med scandinav*, 1936, **lxxviii**, 196-203
- 45 HERRICK, J B On mistaking other diseases for coronary thrombosis, *Jr Med Soc New Jersey*, 1935, **xxxii**, 590-595
- 46 HAMMAN, L Remarks on the diagnosis of coronary occlusion, *ANN INT MED*, 1934, **viii**, 417-431
- 47 WHITE, P D A new record in longevity after coronary thrombosis, *Jr Am Med Assoc*, 1937, **cvi**, 1796-1797
- 48 MASTERS, A M Prognosis in occlusion of the coronary arteries, *Modern Concepts Cardiovascular Disease*, 1936, **v**, No 12
- 49 WHITE, P D Heart disease, 1937, second edition, Macmillan Company, New York
- 50 RISEMAN, J E F, and BROWN, M G Medicinal treatment of angina pectoris, *Arch Int Med*, 1937, **lx**, 100-118
- 51 GOLD, H, KWIT, N T, and OTTO, H The xanthines (theobromine and aminophylline) in the treatment of cardiac pain, *Jr Am Med Assoc*, 1937, **cvi**, 2173-2179
- 52 Report of the Council on Pharmacy and Chemistry Limitations of claims for aminophylline and other xanthine derivatives, *Jr Am Med Assoc*, 1937, **cvi**, 2203
- 53 BROWN, M G, and RISEMAN, J E F The comparative value of purine derivatives in the treatment of angina pectoris, *Jr Am Med Assoc*, 1937, **cix**, 256-258

- 54 EDITORIAL The side actions of barbitals, *Jr Am Med Assoc*, 1937, cix, 508-509
- 55 MASTER, A M, DACK, S, and JAFFE, H L Coronary thrombosis an investigation of heart failure and other factors in its course and prognosis, *Am Heart Jr*, 1937, xiii, 330-361
- 56 GINSBURG, A M, STOLAND, O O, and LOY, D T Studies on coronary circulation the effect of intravenous injections of dextrose on coronary circulation, *Arch Int Med*, 1935, lv, 42-51
- 57 BARACH, A L, and LEVY, R L Oxygen in the treatment of acute coronary occlusion, *Jr Am Med Assoc*, 1934, ciii, 1690-1693
- 58 WIGGERS, C J, and GREEN, H D The ineffectiveness of drugs upon collateral flow after experimental coronary occlusions in dogs, *Am Heart Jr*, 1936, xi, 527-541
- 59 GOLD, H, TRAVELL, J, and MODELL, W The effect of theophylline with ethylenediamine (aminophylline) on the course of cardiac infarction following experimental coronary occlusion, *Am Heart Jr*, 1937, xiv, 284-296
- 60 MIDDLETON, W S Prognosis and treatment of coronary occlusion, *Minnesota Med*, 1935, xviii, 710-724
- 61 BELLET, S, JOHNSTON, C G, and SCHECTER, A Effect of cardiac infarction on the tolerance of dogs to digitalis, *Arch Int Med*, 1934, liv, 509-516
- 62 SMITH, F M The pharmacology of the coronary circulation, *In* LEVY, R L, Editor Diseases of the coronary arteries and cardiac pain, 1936, Macmillan Company, New York, 109-127
- 63 FISHBERG, A M, HITZIG, W M, and KING, F H Circulatory dynamics in myocardial infarction, *Arch Int Med*, 1934, liv, 997-1019
- 64 HADFIELD, G Cardiac infarction, *Lancet*, 1928, i, 189
- 65 HUBBLE, D Angina pectoris and coronary disease, *Lancet*, 1930, i, 908-911
- 66 LUTEN, D Contributing factors in coronary occlusion, *Am Heart Jr*, 1931, vii, 36-44
- 67 LEVINE, S A, ERNSTENE, A C, and JACOBSON, B M The use of epinephrine as a diagnostic test for angina pectoris, *Arch Int Med*, 1930, xlv, 191-200
- 68 MILES, G, and SMITH, P W Effects of epinephrine on the heart, *Am Heart Jr*, 1937, xiv, 198-210
- 69 DOUGLAS, A H, GELFAND, B, and SHOOKHOFF, C Production by epinephrine of S-T changes in the electrocardiogram of the cat, similar to those of coronary occlusion, *Am Heart Jr*, 1937, xiv, 211-218
- 70 LEVINE, S A, and STEVENS, W B The therapeutic value of quinidine in coronary thrombosis complicated by ventricular tachycardia, *Am Heart Jr*, 1928, iii, 253-259
- 71 WHITE, J C Paravertebral injections of alcohol, ganglionectomy and posterior rhizotomy for the relief of cardiac pain, *In* LEVY, R L, Editor Diseases of the Coronary Arteries and Cardiac Pain, 1936, Macmillan Company, New York, 363-386
- 72 MANDL, F Weitere Erfahrungen mit der parvertebralen Injektion bei der Angina pectoris, *Wien klin Wchnschr*, 1925, xxxviii, 759-760
- 73 SWETLOW, G I Paravertebral alcohol block in cardiac pain, *Am Heart Jr*, 1926, i, 393-412
- 74 BLUMGART, H L, LEVINE, S A, and BERLIN, D D Congestive heart failure and
24 angina pectoris The therapeutic effect of thyroidectomy on patients without clinical Jr pathologic evidence of thyroid toxicity, *Arch Int Med*, 1933, li, 866-877
- 25 ANITSCHART, H L Total thyroidectomy for the relief of cardiac pain and congestive Arteriosclerosis, *In* LEVY, R L, Editor Diseases of the coronary arteries and cardiac 322 Macmillan Company, New York, 387-416
- 26 ANITSCHKOW, L CUTLER, E C, and EPPINGER, E C Thyroidectomy in the treatment Bedeutung fur congestive heart failure and angina pectoris, *New England Jr Med*, 1933, u path Anat, 191,
- 27 KRAFKA, J, JR TH EPPINGER, E C Further experiences with total thyroidectomy in 1-19 intractable heart disease, *Am Heart Jr*, 1935, x, 736-761

- 78 BECK, C S The development of a new blood supply to the heart by operation, In LEVI, R L, Editor Diseases of the coronary arteries and cardiac pain, 1936, Macmillan Company, New York, 417-426
- 79 BECK, C S Further data on the establishment of a new blood supply to the heart by operation, Jr Thoracic Surg, 1936, v, 604-611
- 80 MAUTZ, F R Reduction of cardiac irritability by the epicardial and systemic administration of drugs as a protection in cardiac surgery, Jr Thoracic Surg, 1936, v, 612-628
- 81 BECK, C S Coronary sclerosis and angina pectoris treatment by grafting a new blood supply upon the myocardium, Surg, Gynec and Obst, 1937, LIV, 270-272
- 82 O'SHAUGHNESSY, L F Surgical treatment of cardiac ischemia, Lancet, 1937, I, 185-194
- 83 BECK, C S Personal communication to the author

THE MECHANISM OF HEAT LOSS AND TEMPERATURE REGULATION*

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THERE have been surprisingly few studies dealing with the mechanism of heat loss. Heat production has received more than its share of consideration because it is really the balance between production and loss that determines the body temperature.

The Russell Sage Institute of Pathology happens to possess a respiration calorimeter which measures production and loss from the human body simultaneously but independently. This instrument, which was moved from Bellevue Hospital to New York Hospital in 1932, has been used in the study of patients with fever and many normal controls under varying atmospheric conditions. We directed our attention almost entirely to production until about 1929 when we began to realize that it was necessary to study the details of heat loss. The factor of loss by conduction of heat through solid bodies was so small in our calorimeter bed that it could be neglected. Likewise, the factor of warming food was insignificant. Vaporization of water from skin and lungs which usually accounted for about one-quarter of the heat loss was easily measured. Radiation and convection which accounted for the remaining three-quarters presented great difficulties. We measured them together but could not separate them until 1934 when Dr James D Hardy perfected his radiometer and surface thermometer.

The human body under ordinary conditions loses about 60 per cent of its heat by the radiation of infra red waves which travel in straight lines with the speed of light until they strike the walls of the calorimeter or room. The amount of radiation depends on the profile surface of the body and the average temperature difference between the surface of the skin and the walls. It can be measured by determining the radiating temperature of 20 different spots on the body and the radiating temperature of the walls. Using the Hardy radiometer this can be accomplished in two or three minutes. When the calories lost in radiation are subtracted from the total lost by radiation plus convection we measure the convection by difference. Convection currents of air caused by the warmth of the body remove about 12 to 15 per cent of the total heat when a man is quiet. If he exercises the increased fanning effect may double or triple the amount of heat lost in warming the air.

On the basis of a large number of detailed studies in the calorimeter it has been possible to construct a diagram which represents a balance with

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heat production on the left pan and heat loss on the right. When the two are in equilibrium the pointer rests at 37°C . When the pans are unequally weighted the pointer swings to abnormally high or abnormally low temperatures. The load of heat production rests on the supporting legs of carbohydrate, fat, and protein, since it is only through the combustion of these substances that heat production is possible. The load of heat loss rests on the factors of convection, radiation, and vaporization.

Under basal conditions the loads on the two pans are small and are easily balanced. Moderate increases in the heat production may be caused by the stimulating effects of food, so-called specific dynamic action, by disease, if accompanied by a higher metabolism, or by the unconscious tensing of the muscles caused by emotion or by an approaching chilliness. Of

FACTORS INCREASING

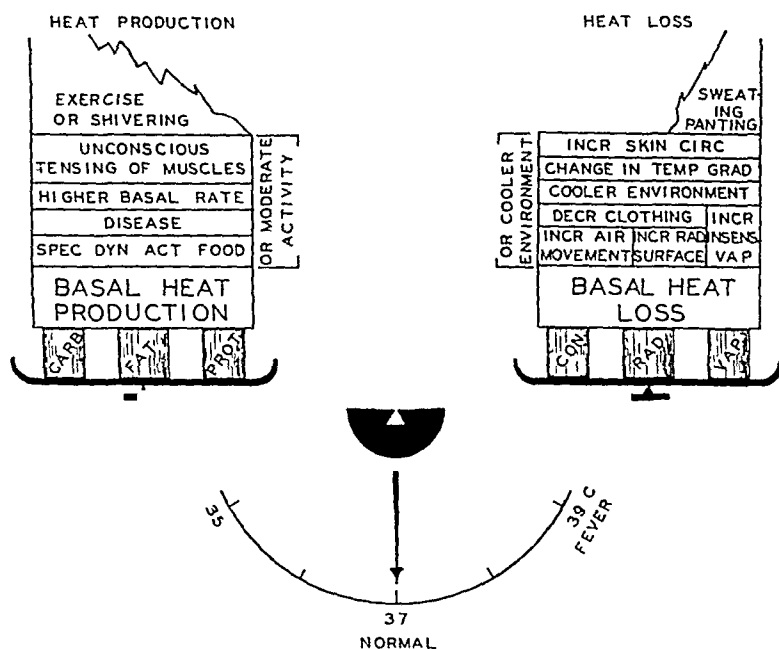


FIG 1 Balance between the factors increasing heat production and heat loss

course the moderate increases in heat production are ordinarily due to moderate muscular activity.

Usually these moderate increases in heat production are nicely balanced by factors increasing heat loss. The man decreases the amount of clothing, seeks a cooler environment or a place where there is increased air movement. Children spread out arms and legs to extend the radiating surface. With augmented heat production the insensible vaporization from skin and lungs increases with equal pace. If these adjustments are not sufficient the body is able to lose more heat by increasing the circulation in skin and subcutaneous tissue, thus changing the temperature gradient and bringing warm blood close to the surface. Although this flushing of skin is striking both

to subject and clinical observer the effect is limited, as a rise of one degree in skin temperature in the average sized man at ordinary room temperature can account for an extra loss of only 14 calories per hour

It is interesting to consider what happens when a balance which has been established under basal conditions is disturbed by a moderate rise in heat loss, due to cooling of the environment or decreased clothing or any of the other factors which we have indicated on the right hand of the diagram. The body does not respond by a higher basal rate but there is, after a short delay, a higher total metabolism due to conscious or unconscious use of the muscles. If the increased heat loss be considerable the balance will swing and the pointer indicate a subnormal temperature. This can be corrected only by violent exercise or by shivering.

If, on the other hand, heat loss has remained constant and heat production has been raised suddenly by violent exertion, such as running, the factors of heat loss which were sufficient under moderate conditions are no longer capable of maintaining balance. Body temperature rises slightly, and then there is a sudden outbreak of sweat. It is the great rise in vaporization that restores the balance. Increased convection helps a little, but inasmuch as the skin temperature falls, radiation is diminished.

Another set of conditions occurs in hot weather. As soon as the temperature of the air and of the surroundings rises to a level which equals surface temperature, 35°C (95°F), radiation and convection cease to function as channels of heat loss. Vaporization must bear the entire burden no matter how small or how great the heat production. If the humidity be high vaporization is suppressed and body temperature rises. This is a fairly good combination for producing artificial fever but there is a better one. If the temperature of the air and walls be raised above that of the surface of the body, the gradients are reversed and the usual factors of loss are turned into factors of gain.

How is it that under ordinary conditions of life body temperature is maintained so nicely at 37°C , a little lower in the morning, a little higher in the evening? There is probably a good deal of local adjustment in various parts of the body but the finer control seems to be in the hypothalamus. In disease the thermo-regulator may suddenly be set at a higher level. Suppose in our balance diagram the body established a new "normal" at 39°C . The pointer at 37°C would then be two degrees too low and the body would suddenly need about 120 calories in order to bring the temperature of the mass of tissue up to this new level. The only way it could accomplish this rapidly would be by shivering. Once the body had been warmed to the new level another balance could be established. If the change in the adjustment of the temperature regulating center be made slowly, shivering is not necessary, as minor adjustments in the factors increasing heat production or decreasing heat loss can accomplish a change of 2°C in a few hours.

The result of a sudden increase in heat production is well demonstrated in a diagram showing what happened in a game of squash lasting 36 minutes. Two of the staff who were excellent players and evenly matched were studied at 12 minute intervals during exercise and the period of recovery. Figure 2 shows the results on one man who had served as a normal control in many calorimeter experiments. The rectal temperature, skin temperature, and

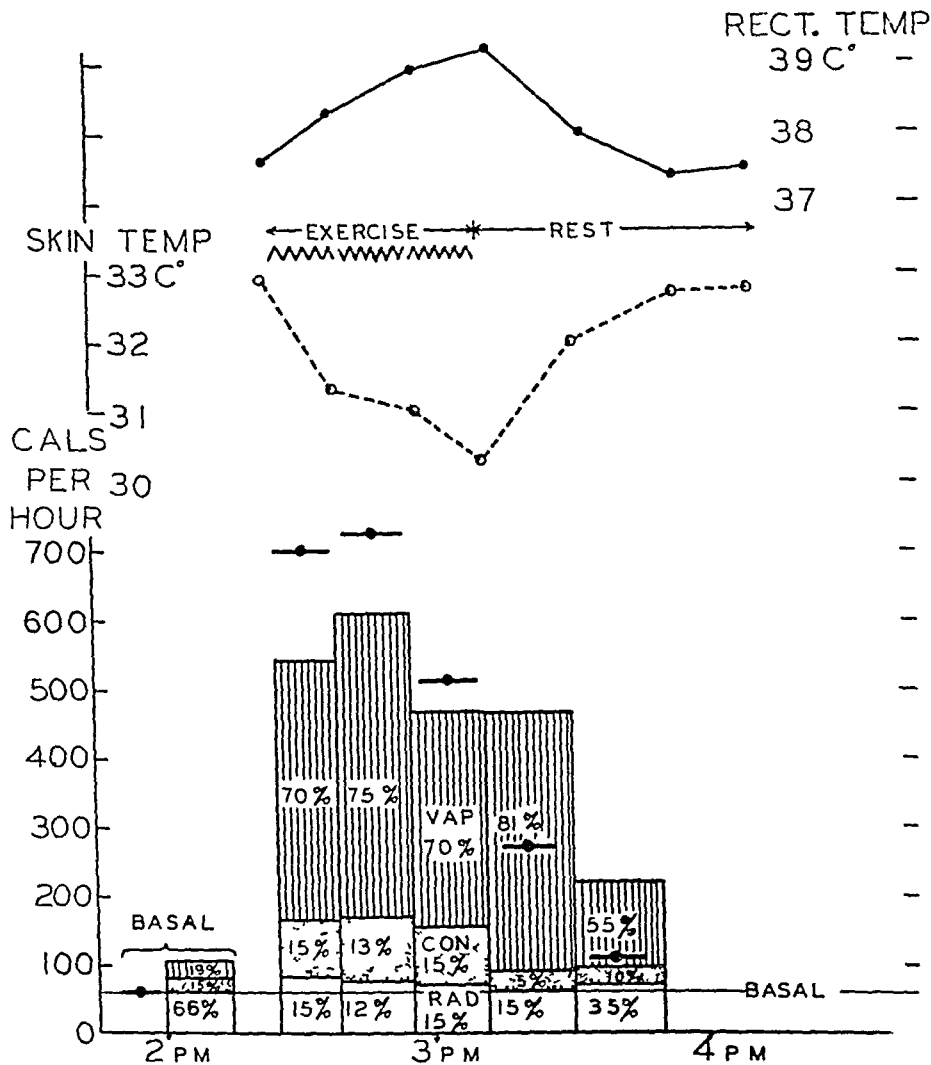


FIG 2 Violent exercise in 36 minutes of squash racquets as shown by zig zag lines. Heat production is indicated by dots with short horizontal lines, heat loss by columns divided into radiation, convection, and vaporization. Note rise in rectal temperature and fall in skin temperature with rapid restoration to normal.

radiation were determined accurately. On the diagram the short horizontal lines with dots in their centers represent heat production, the columns show heat loss divided according to our estimation of the amounts dissipated in radiation, convection, and vaporization. During exercise heat production exceeded loss by such a great margin that the rectal temperature rose to

39° C After the game the players rested, the loss exceeded the production, and the temperature fell to normal almost as rapidly as it had mounted. The skin temperature dropped with the first outbreak of sweat and continued to fall rapidly. This meant that the total heat lost in radiation was actually diminished although the skin was flushed with blood. Convection was increased as the man rushed about the court but it was evident that vaporization had to account for 70 to 80 per cent of the loss. The cooling must have taken place very close to the surface as the subcutaneous tissue was

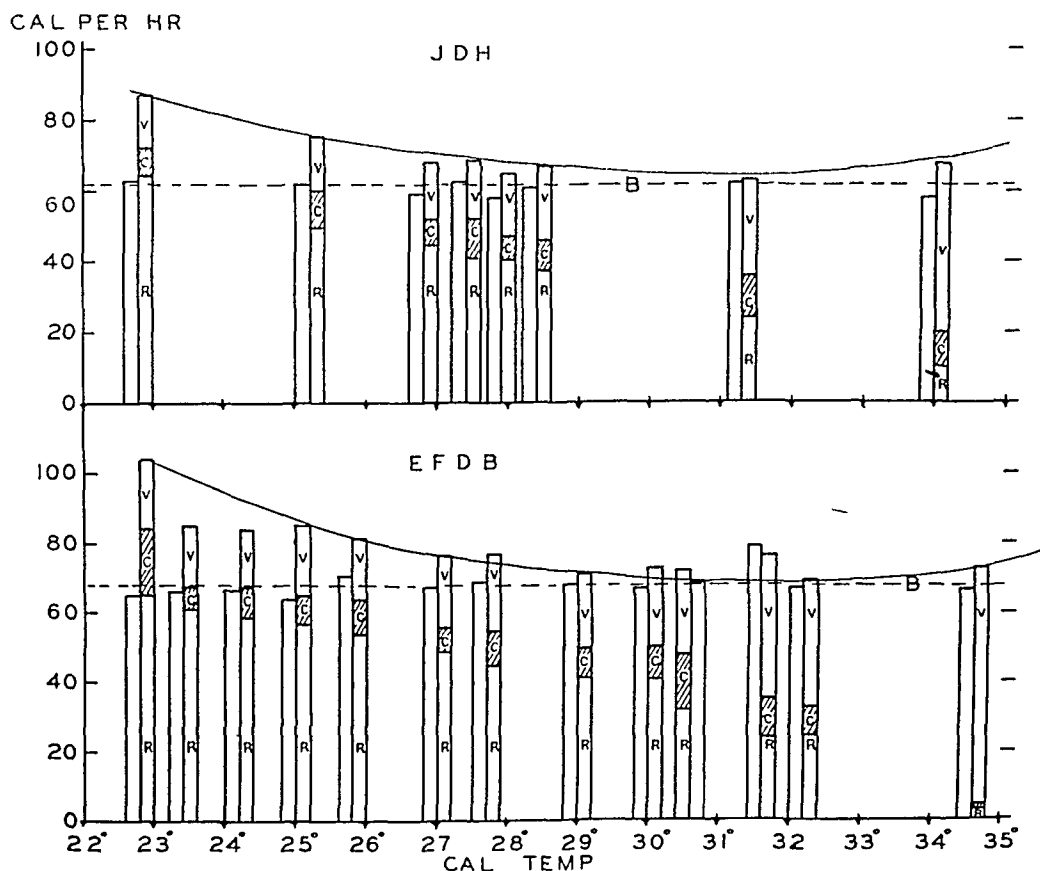


FIG 3 Heat production (blank columns) and heat loss (columns divided to show radiation, convection, and vaporization) of two normal men, naked, under basal conditions in the calorimeter, exposed to air at temperatures between 22° C and 35° C. The dotted line B shows the average basal metabolism.

receiving blood at a temperature of 39° C while the surface temperature averaged 31° C, a gradient of 8° C in a few millimeters. When the game started the difference between rectal temperature and skin temperature had been only 4.5° C.

We have made a series of studies on naked normal controls at temperatures from 22° C to 35° C. Figure 3 shows the results on a man under basal conditions. His heat production was the same throughout

the range in spite of the fact that he was on the verge of shivering at 22°C and was losing all of his heat through sweating at 35°C . His proportion of heat lost by radiation decreased steadily as the difference between skin and wall temperature diminished.

When a man is exposed naked and motionless and empty of food to ordinary room temperature he loses much more heat than he produces and his skin and subcutaneous tissues become colder and colder. The rectal temperature begins to fall. When a certain amount has been lost the temperature regulating center urges the man to exercise and if he, for experimental purposes, remains quiet the center will suddenly call for a chill. Figure 4 shows that under normal conditions the chill came after the average body temperature had dropped about 0.7°C . In three experiments a drink of brandy postponed the chill and allowed the body to cool off, perhaps to a

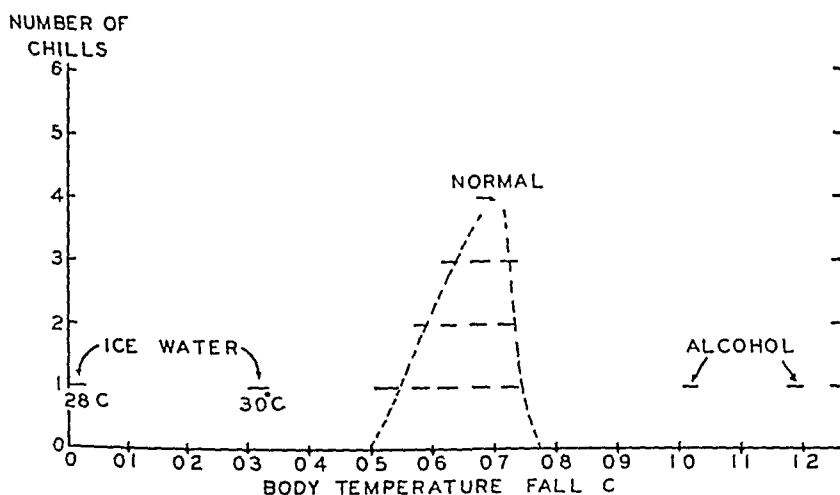


FIG. 4. Diagram showing the fall in the average body temperature before the onset of a frank chill. Under normal conditions the chill comes after a drop of about 0.65°C . Alcohol postpones the chill, ice water in the stomach precipitates a chill abruptly.

dangerous extent. In one experiment a drink of ice water given to a woman who was not due to have a chill for about two hours precipitated shivering before the body temperature had time to drop more than 0.01°C .

Chills resulting from excessive cooling of the body resemble in almost every respect chills which occur at the onset of fever. Figure 5 shows what happened after an exposure, naked, in the calorimeter at 22°C . The average skin temperature fell to 29.5°C , the rectal temperature fell 0.4°C , and the average temperature fell 0.73°C . There was a sudden chill lasting 18 minutes and this raised the skin temperature until the man was fairly comfortable. Skin temperature dropped again and a second chill caught him as he was being taken out of the calorimeter.

I cannot help showing once more the results obtained in 1918 by Dr David P. Barr and myself on the patient George S. who kindly obliged us by having a malarial chill in the calorimeter. When the chill came the heat

production increased from 80 calories to 230 calories an hour, but the heat loss was maintained at the previous basal level. All the extra heat was stored in the body. The temperature was raised to 41°C and balanced at this point for an hour or so. Then the temperature regulator was apparently readjusted to a normal of 37°C and the body, finding itself 4° too warm, poured out sweat until vaporization had cooled the tissues.

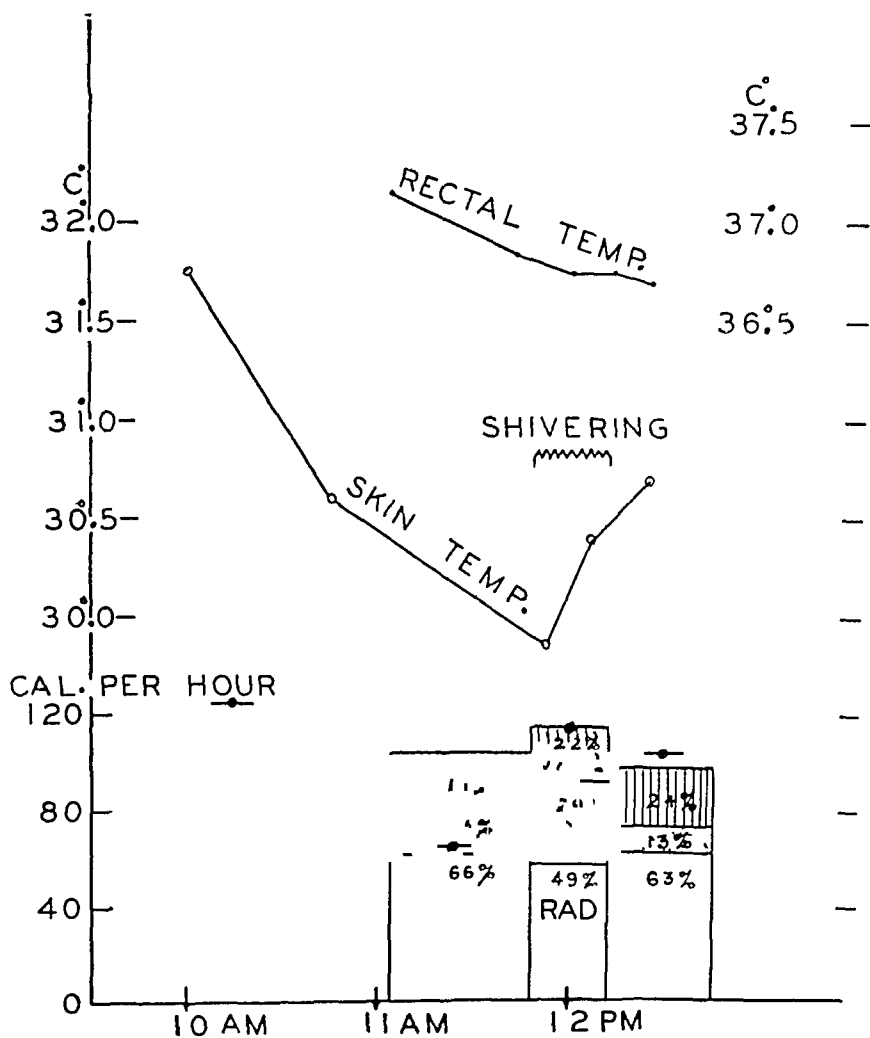


FIG 5 A chill caused by exposing a naked man to a temperature of 22°C . Heat production indicated by dots with short horizontal lines. Heat loss in columns.

Throughout this paper I have repeatedly called attention to the fact that the skin is responsible for almost the entire heat loss. It is beautifully constructed and beautifully regulated for this purpose, and if you study it carefully you can find out what the body is doing. There is an old dictum that it is easy to measure skin temperature but hard to know what to do with the results. Dr. Hardy says that it is very difficult to measure skin temperature accurately but the results give much information. He has

demonstrated that the older methods of estimating skin temperature by thermocouples placed in contact with the skin are unphysiological and inaccurate. It is impossible to estimate the average temperature of the surface unless readings are made in many places, and the most deceptive places to measure are the hands and feet. The hands respond too quickly to emotion, the feet cool off too rapidly. Often we have found in normal persons with no change of rectal temperature a marked drop in the temperature of the toes until they were cooler than the surrounding air. On one occasion during a chill we obtained several readings of skin temperatures higher

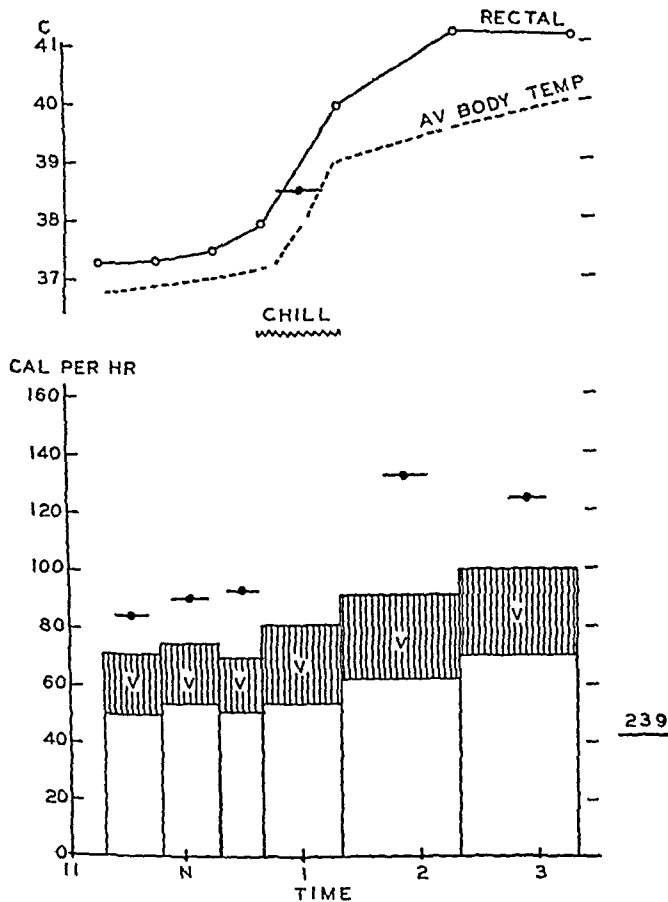


FIG 6 A malarial chill. A redrawing of the diagram of the patient George S. studied by Barr and Du Bois.

than rectal temperatures. It is necessary to remember that a man of average size has about 15 kg of tissue within one centimeter of the surface. This surface layer may change its temperature at a different rate and even in a different direction from the rectal temperature. After all, the rectal thermometer or the mouth thermometer only tells us what is happening in one small area during a few minutes of the day and gives the clinician merely an approximate idea of what has been accomplished as the body tries to balance or readjust heat production and heat loss.

CASE REPORTS

LYMPHATIC LEUKEMIA OF TWENTY-FIVE YEARS' DURATION*

By CHARLES W. MCGAVRAN, B.S., M.S., M.D., F.A.C.P., *Columbus, Ohio*

THE following is a report of a case of chronic lymphatic leukemia and associated with it, a mild diabetes and a progressive cardiovascular disease. It is of unusual interest because of the duration of life after the discovery of the leukemia. Data concerning the duration of life after the onset of chronic lymphatic leukemia are quite meagre. Minot and Isaacs⁴ in 1924 report on the duration of life in 87 cases the longest of which was under observation 22 years. The case here reported was observed 25 years and all this time the patient was under the personal observation of the author.

F. C. first presented himself on December 21, 1905, at the age of 48. He was married and a banker. During a recent life insurance examination, sugar had been found in the urine. He was apprehensive and complained of a sense of fullness in the epigastrium accompanied by acid eructations. His father had died at 70 of cancer of the stomach and his mother at 70 from congestive heart failure preceded by hypertensive heart disease. There were three brothers, one of whom died of spinal meningitis and a second one who died of tuberculosis at the age of forty-five. The third was living but asthmatic. There were two sisters, one of whom died in infancy of pneumonia and the other was living and healthy. His previous health was good. He had had no serious illness. At the age of 33, he had suffered from eczema followed by a series of boils. His height was 5' 8", weight 185½ pounds. Blood pressure was 154 systolic and 70 diastolic. His chest was large. Cardiac dullness was well within normal limits. Heart tones were clear. Lungs were negative. Abdomen was large.

During the five succeeding years, he was seen only occasionally. He had two or three attacks of acute bronchitis. He had a tremor to his hands which persisted throughout his life. During December of 1910, sugar was again found in his urine and it persisted throughout the month, varying from 1 to 2 per cent.

Because of his indigestion manifested by acid eructations and a sense of fullness in the epigastrium which progressively increased in intensity, he was referred on January 24, 1911, to the late Dr. John H. Musser of Philadelphia, who reported as follows: "He has intermittent glycosuria, which is, in all probability, secondary to a sclerotic pancreas and liver associated with and perhaps dependent upon cardiovascular conditions. It is interesting to note a leukocytosis of 18,960, and a great increase of lymphocytes, as follows:

Polys	36%
Small lymphs	42%
Large pale mono	
Transitional	20%
Eosinophiles	2%

* Received for publication September 23, 1937

This is a lymphatic type of leukemia which I have seen accompanying intermittent glycosuria or, perhaps, better say, intermittent glycosuria as seen in lymphatic leukemia"

On January 29, 1911, he was seen by Dr E P Joslin of Boston who reported as follows

" Hemoglobin	100%
White blood count	23,200
Differential count of 200 cells	
Lymphocytes, mostly large	93%
Polynuclears	5%
Transitional	2%
No blasts or stippling	
Nothing abnormal with the reds	

"The exact proportion of the white corpuscles evidently varies somewhat from day to day I am not especially apprehensive of this finding in Mr C's case and have said nothing to him about it I think that it would be well to examine the blood again in the course of a month My physical examination corresponds in general with what had been previously observed The left border of the heart was 1 cm inside the mammillary line, no murmurs, and I made the blood pressure 150 mm mercury There were no palpable cervical, axillary or inguinal lymph nodes The abdomen was negative except that I could just touch the spleen and, therefore, considered it a little large"

Both consultants recommended that nothing be said to the patient about his blood condition, that no therapy of any kind be attempted and that his blood be examined at rather infrequent intervals and the symptoms be treated as they developed Dr Joslin saw him every few years and directed the line of management

In March 1917, Dr Joslin referred the patient to Dr George R Minot of Boston who reported in part as follows

" Hemoglobin	100%
Red count	5,100,000
White count	25,500
Platelets	160,000
Differential count of 400 cells excluding 'smudges'! (If these were counted and considered of lymphoid origin, note that the percentage of lymphocytes would be higher)	
Polynuclear neutrophiles	19%
Small and medium lymphocytes	68%
Large lymphocytes	8%
Large mononuclear cells	4.2%
Eosinophiles	0.5%
Mast cells	0.2%

"I am inclined to consider the condition chronic lymphatic leukemia on account of the continued elevated and gradually rising white blood cell count over a period of six years with persistent and apparently increasing lymphocytosis and on account of the abnormality of many of the lymphocytes The diminution of the platelets also favors this diagnosis I am rather inclined to believe that, as the process seems to have been so chronic and relatively mild, it will continue a long time without much additional severity although, I suppose, it is equally possible that it might 'burst into flame' at any time and become severe and more rapidly progressive I do not see that there is any treatment for the blood condition that would be of any benefit or distinct advantage at the present time I am rather inclined to believe that it would be better to leave things alone and not stir them up"

In 1911, the spleen could just be touched on deep inspiration It gradually increased in size but was never larger than to extend three fingers below the costal

margin It always became smaller and less distinctly palpable following irradiation which was first given in June 1926 For many years, there were no palpable superficial lymph nodes In April 1917, the inguinal nodes were first palpable, the size of a bean They gradually increased in size but never became larger than a hazel nut In 1918, one small lymph node, the size of a B B shot, was just palpable above the left clavicle At the same time, the axillary nodes became palpable, the size of a bean They remained palpable thereafter but did not increase in size In May 1927, in making a rectal examination, a node, the size of a hazel nut, was felt just posterior to the prostate There was never a noticeable increase to its size

Very soon after the leukemia was discovered, the patient began to have looseness of the bowels These attacks were usually controlled by dietary regulation and castor oil Later it was necessary to give a mild opiate from time to time In May 1926, the diarrhea had become very severe The remedies which had formerly helped him gave him no relief He lost much in weight and was quite weak

He was again seen by Drs Joslin and Minot and Dr Minot reported as follows "I am strongly inclined to believe that the diarrhea, which he has, is directly dependent upon his leukemia It is, I think, not at all unusual for these patients to develop the sort of diarrhea he has had dependent upon leukemic lesions throughout the small intestines I noticed a considerable number of young lymphocytes rather large in size, which broke up very readily There occurred a few lymphoid-blasts and about 10 per cent definitely abnormal immature forms of lymphocytes Among the smaller lymphocytes, I noticed signs of youth I found only about 5 per cent polynuclears, 7 per cent cells which may have been monocytes, the remaining cells, except for a very rare eosinophile, were lymphocytes of all ages, there being rather more immature ones than normal ones This blood picture suggests to me an increased activity of his disease in recent months This is consistent with what I think is taking place within the intestinal tract By and large, he seemed in very good condition but I feel sure that it would be wise for him to have at least one full sub-erythema dose of deep roentgen-ray I advise this to be given over the splenic area, the total sub-erythema dose being divided into four treatments Then three or four weeks thereafter, if improvement has not occurred, I should advise another sub-erythema dose over the chest, aiming simply to irradiate a large blood area "

IRRADIATION

In June 1926, he received the deep roentgen-ray therapy as directed The diarrhea responded immediately The white blood cell count came down gradually from 67,500 on June 9, to 35,000 on July 1, and 22,000 on July 29 He felt very much better and spent the winter in California and the summer of 1927 in England In September 1927, the diarrhea returned and he was again irradiated This course of treatment was followed by a marked fall in the white blood cell count On September 22, 1927, the white blood cell count was 44,000 and on the fourteenth of October, 7,000 with polynuclears 32 per cent and lymphocytes 68 per cent The diarrhea again responded and he felt much better in every way The irradiation was repeated in September 1929, again in 1930, 1932, and in 1934 These treatments were always followed by a marked fall in the white cell count, an abatement of his diarrhea and an improvement in his general condition His skin, which was usually dry and scaly, would become moist and soft At the time of his death, Mr C was doing well from the standpoint of his leukemia The last blood examination, made one year after the last irradiation or two months before his death, showed the white blood cells to be 12,000 with 86 per cent lymphocytes

In January 1932, Mr C was examined by Dr B K Wiseman of the College of Medicine of the Ohio State University Dr Wiseman found that the lymphatic curve, which when normal (according to previous studies¹) illustrates that in lymphopoiesis the lymphocytes are delivered to the peripheral blood in half-hour cycles,

was completely arrhythmic as is usually found in leukemic states² The analysis of the qualitative aspects of the lymphocytes indicated an average Y-M-O (young-mature-old) formula of 13%-48%-39% (normal 5%-47½%-47½%) with many pathologic types of lymphocytes similar to those found in other cases of chronic lymphatic leukemia

The accompanying chart shows the high and low percentage of hemoglobin found each of the 25 years and records the high and low white blood cell count, percentages of lymphocytes, and body weights for the same period It is needless to say that there were many other blood examinations made It is to be noted that the leukemia progressed very slowly and had it not been for his cardiovascular complications, Mr C would probably have lived for many more years

ANEMIA

Throughout the first 15 years of observation the patient's red blood cell picture was normal Whether coincident or not, signs of anemia appeared in 1926 following the first irradiation On June 10, 1926, before the first roentgen-ray therapy, the

Date	Hemoglobin (Sahli) %	White Blood Count 1000 cu mm	Lympho- cytes %	Weight Lbs
1911 High Low	100 80	24 7 14 3	95 62	182 166
1912 High Low	95 90	27 1 19 2	84 5 78	170 163
1913 High Low	100 85	29 25 2	88 77	171 162
1914 High Low	90 90	29 2 26	90 3 77	175 168
1915 High Low	97 90	35 18	92 86	171 165
1916 High Low	112 92	34 6 26 4	89 85	163 162
1917 High Low	100 87	34 25 5	91 80	166 160
1918 High Low	100 85	32 8 24 2	87 76	161 160
1919 High Low	98 87	43 7 25	95 84	171 162
1920 High Low	100 100	41 32 7	90 88	170 167
1921 High Low	100 100	31 26	90 88	160 156
1922 High Low	100 95	46 22 7	89 84	164 159
1923 High Low	100 95	41 26	97 87	160 157

Inguinal lymph nodes palpable

(Chart continued on next page)

Date	Hemoglobin (Sahli) %	White Blood Count 1000 cu mm	Lympho cytes %	Weight Lbs	
1924 High Low	100 92	38 4 29	95 90	159 157	Angina
1925 High Low	100 90	47 7 33	95 86	156 151	
1926 High Low	100 74	70 22 1	96 90	146 138	Diarrhea Roentgen-ray therapy
1927 High Low	100 84	44 7	96 68	143 139	Roentgen-ray therapy
1928 High Low	94 83	26 7 10	90 80	150 144	Roentgen-ray therapy
1929 High Low	92 78	51 29	96 90	153 150	Coronary thrombus
1930 High Low	100 80	24 1 19 4	93 87	153 150	Roentgen-ray therapy Congestive heart failure
1931 High Low	91 82	35 14	95 89	167 145	Roentgen-ray therapy
1932 High Low	92 70	57 7 25	98 90	150 149	Roentgen-ray therapy
1933 High Low	90 79	69 38	97 92	150 149	
1934 High Low	90 65	112 16	89 90	142 140	Roentgen-ray therapy
1935 High Low	85 72	22 2 12 4	96 86	143 140	

blood examination showed a hemoglobin of 97 per cent and a red cell count of 4,775,000. He was then irradiated and anemia developed progressing to a maximum on July 15, at which time the hemoglobin was 74 per cent and the red cell count was 3,640,000. This anemia persisted throughout the rest of his life with remissions and exacerbations. At times, the blood picture was hyperchromic in nature and, for this reason, liver therapy was tried but without favorable response. Iron therapy was then instituted in the form of 60 grains of Bland's mass a day which was always effective.

DIABETES

In February 1911, his glucose tolerance was determined by Dr E P Joslin who pronounced him a mild diabetic. He was sugar-free upon a diet containing 170 grams of carbohydrates. He was instructed concerning the carbohydrate, protein and fat value of foods, he was also instructed to reduce in weight and to live on a diet which would not permit him to weigh over 170 pounds. Daily out-of-door exercise was advised and it was recommended that he take yearly winter and summer vacations. Thereafter, Mr C was an ideal patient. He watched his diet carefully and did not gain in weight. He walked six miles a day and played golf frequently. This exercise was continued until his cardiovascular system no longer permitted it. He usually rested after his noon-day meal. The vacations were taken as prescribed.

In fact, all through the remaining 25 years he cooperated in every way. Because of his complete cooperation, his diabetes never presented any unusual problems. He is reported by Dr Joslin case No 393.³

CARDIOVASCULAR DISEASE

As early as 1905, at the age of 48, the patient showed evidence of hypertensive heart disease. This condition slowly but gradually became more pronounced. The blood pressure became higher and the heart larger. In 1917, cardiac dullness extended to a point 1 cm. external to the left nipple. He had faithfully carried out his instructions as to daily exercise, walking and golfing when the weather permitted. In June 1924, he began to complain of dizziness. In September of that year he had precordial pain after exercise. The pain radiated to the shoulders and down the arms. He was informed as to the cause of this pain and was instructed to recognize his limitations and to stay within them. This meant limiting his daily walks. He was furnished with a supply of nitroglycerin tablets (hypo), grains $\frac{1}{100}$, and was told to carry them with him at all times and to dissolve one under his tongue in the event of pain. Later, aminophyllin, grains $1\frac{1}{2}$ after each meal, was prescribed. He did not worry about his condition and to the best of his ability attempted to carry out instructions. He had occasional attacks of pain. In August 1928, while in Canada, he had a severe attack of angina. He was seen by Dr Robert Sterling Palmer of Boston who reported, "arteriosclerosis and hypertensive heart disease with anginal failure."

In November 1929, he had a very definite coronary thrombus and one month later, while still confined to his home, he had a second thrombus which nearly caused a fatal issue. Both of these attacks began with weakness, faintness, nausea and vomiting. The face was anxious, the skin was cold, moist and ashen gray in color. The radial pulse was scarcely perceptible early in the attacks. The blood pressure was lowered, the heart tones were diminished in intensity. No friction sound was heard over the precordium at any time, the thrombus evidently extended inwardly. (This probably accounts for the kidney infarcts which were never recognized clinically.) (See autopsy report.) Pain was not a factor in either attack. He recovered slowly under rest, morphine and aminophyllin. Thereafter, he was a weakened man. His activities were greatly reduced and he suffered little from angina.

Early in 1930, he began to show signs of congestive heart failure manifested by dyspnea and edema of the lower extremities. He was given digitalis, at first two units a day and later, one-half unit a day. He lived solely because he recognized his limitations and stayed within them. On November 29, 1935, Mr. C. went to his office apparently feeling well for him. At 11:30 o'clock he had his luncheon and lay down on his couch to rest. A few minutes later his secretary found him dead.

A complete autopsy was performed by Dr. H. B. Davidson of the Pathology Department of the Ohio State University. The following is a summary of the findings:

- 1 Chronic lymphatic leukemia as evidenced by leukemic changes in lymph nodes, spleen, bone marrow, lungs, pericardium, liver, bladder and prostate.
- 2 Generalized arteriosclerosis, and generalized arteriolar sclerosis.
- 3 Cardiac hypertrophy and dilatation. Myocardial degeneration, fatty infiltration, and fibrous replacement.
- 4 Thrombosis of right coronary artery. Complete obliteration of the anterior descending branch of the left coronary artery below a point 2 cm. from its origin.
- 5 Senile arteriosclerotic nephritis.
- 6 Healed infarcts of each kidney.
- 7 Medullary hyperplasia of the adrenals.
- 8 Benign prostatic enlargement.

- 9 Atrophy and fatty infiltration of pancreas
- 10 Healed childhood tuberculosis
- 11 Bronchiectasis

COMMENT

First, the duration of the leukemia after discovery was 25 years, which the author believes to be the longest survival period recorded

Second, the duration of the leukemia prior to its discovery in 1911 is unknown because of no record of blood examination before that date. It should be noted, however, that besides the diarrhea, the only symptoms of the leukemia that the patient presented were a sense of fullness in the epigastrium and acid eructations and he complained of these symptoms when he first consulted the author in 1905

Third, it is the writer's opinion that the patient lived through all of these years largely because of his complete cooperation with his physicians

Fourth, the diagnosis of cardiovascular disease, made as early as 1911 by the late Dr John Musser, is worthy of comment

Fifth, the response of the diarrhea to the irradiation was quite remarkable

REFERENCES

- 1 SABIN, CUNNINGHAM, DOAN and KINDWALL Normal rhythm of the white blood cells, Bull John Hopkins Hosp, 1925, *xxxvii*, 14
- 2 WISEMAN, B K Personal communication
- 3 JOSLIN, E P Treatment of diabetes mellitus, 5th ed, 1935, Lea and Febiger, Philadelphia, page 408
- 4 MINOT, G B, and ISAACS, R Lymphatic leukemia, age, duration, and benefit derived from irradiation, Boston Med and Surg Jr, 1924, *cxi*, 1

PAROXYSMAL HEMOGLOBINURIA WITH REPORT OF A CASE

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THE term "hemoglobinuria" is used to designate the excretion of blood pigment in the urine with total absence of red blood cells or with only a relatively small number that cannot be considered sufficient to explain the altered, bloody or dark blood like, appearance of the specimen

This phenomenon is observed (1) when hemoglobin in sufficient quantity is injected into the blood stream, (2) after procedures resulting in solution of the red blood cells, such as transfusion of blood, or the injection intravenously of incompatible blood serum of another species, of distilled water, glycerine, oil or many other chemical substances, (3) after certain organic or inorganic poisons have made their way into the blood stream in sufficient quantities, whether from the intestinal tract or through the skin and mucous membranes, following either ingestion, inunction or injection. The list of such poisons includes a number of substances used for therapeutic purposes, e g, chlorates,

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phenol, glycerin, tincture of iodine, sulfuric acid, hydrochloric acid, gumme, etc., (4) after extensive burns, and in consequence of certain severe infections, such as scarlet fever, erysipelas, typhoid fever, pernicious malaria, (5) in certain severe hemolytic anemias when hemolysis is unusually rapid and extensive, for example in sickle cell anemia and in Lederers anemia, (6) lastly, in *periodic* or *paroxysmal* (intermittent) *hemoglobinuria*, a peculiar chronic affection in which hemoglobin appears in the urine at intervals accompanied by a characteristic clinical syndrome

The development of our present knowledge of this rare condition, paroxysmal hemoglobinuria, has been gradual. A number of men have contributed descriptions of features of the syndrome which are now considered essential to its recognition. Diessler described a patient with intermittent bloody urine in 1854 and noted that the color was due to hemoglobin in solution and not to whole blood. Pavy in 1866 differentiated hemoglobinuria of the paroxysmal type from that occurring in connection with malaria. Gull in the same year described the effect of chilling in bringing on an attack. Rosenbach (1880) showed that by placing the patient's feet in ice water an attack could be artificially produced. Kussner (1879) by observing the blood serum during an attack demonstrated that hemoglobinemia accompanied the hemoglobinuria. Muir (1880) called attention to the association of paroxysmal hemoglobinuria with syphilis, evidences of which he found present in nearly 50 per cent of the reported cases. In 1881 Ehrlich showed that hemoglobinemia was produced locally at the site of chilling, the immersion in ice water of a finger about the base of which a ligature has been placed led to hemolysis of the blood within the vessels of this finger. He felt that a hemolysis was produced by the chilled tissues. In 1904 the mechanism of the disease was further elucidated by Donath and Landsteiner whose experiments indicated that in patients with this disease an auto-hemolysis is present which acts in two phases (1) union of the lysis with the red corpuscles at low temperatures, and (2) lysis of the red corpuscles so attacked, when the temperature again rose to normal. Complement is necessary for the reaction. Since that time numerous workers have studied this mechanism and added to our knowledge of factors which qualify the behavior of the auto-lysis, the essential observations, however, have all been confirmed.

Study of the case reports since the introduction of the Wassermann test has shown that syphilis is present in well over 90 per cent of cases which exhibit the other criteria of paroxysmal hemoglobinuria. Congenital syphilitics are more prone to the condition than cases of acquired syphilis. Sufficient evidence has now been gathered to prove that effective antiluetic therapy will usually result in disappearance of the attacks of hemoglobinuria. It has become apparent that the degree of chilling necessary to initiate an attack is not the same in all cases. Exertion has also been shown to precipitate hemolysis in some cases of the disease, and in certain instances it is possible that acute emotional disturbances may have a similar effect. Cases of paroxysmal hemoglobinuria have now been described in most countries and races of the world and at all ages. It is a very rare condition as shown by its low incidence even in large hospital clinics. In its milder forms it is probably often overlooked or misinterpreted.

Paroxysmal hemoglobinuria is essentially a chronic condition with episodic acute attacks of varying severity. In the interval between attacks the patient's

state of health will depend upon the nature and activity of the underlying syphilitic disease and upon the degree of depletion and anemia induced by the preceding attacks of hemolysis. The incidence of the attacks is greater in cold weather. Exposure to cold and wetting of the hands and feet in cold water are the most important precipitating factors.

The duration of the attack is from half an hour up to three or more hours. It is frequently ushered in by a chill, which is followed by a fever rising at times to 104° F. There is often a dragging pain in the back, running down into the thighs, pallor of the skin, and later cyanotic discoloration of the finger tips, toes, and ears. Lassitude, a tendency to yawning, oppression, nausea, pain in the hypochondrium, and occasionally neuralgic pains in the extremities have been observed. The fever is followed by sweating and subsidence of the subjective symptoms.

A macular hyperemia with urticarial wheals may be seen during the attack. Pargnes reported a case in which urticaria could be produced by cooling the hands, the wheals, of a peculiar reddish color, lasting for two hours or more.

Examination of the patient during convalescence from an attack may show evidence of slight enlargement of the spleen and liver, and slight icteric discoloration of the skin and mucous membranes.

The urine during the attack appears bloody or dark reddish brown. On spectroscopic examination it shows the presence of oxyhemoglobin, or methemoglobin and occasionally of other blood pigments. On microscopic examination amorphous blood pigments in granules or irregular masses, or in the form of casts are found but few if any red blood corpuscles. In addition, the urinary sediment often contains hyalin and granular casts, renal epithelium, and cells, the nuclei of which are also stained red. The urine always contains albumin and often bile pigment, but bile acids are absent. As the attack subsides the urine gradually becomes paler, until it resumes its normal color, but albumin remains present for a few days. The appearance of albumin may precede the discoloration. The excretion of hemoglobin is dependent upon the degree of hemoglobinemia and the kidney threshold for hemoglobin, factors which vary with the individual and with the particular attack.

It has been shown that following the attack the hemoglobin in the blood plasma rapidly disappears with a corresponding rise in blood bilirubin and somewhat later an excess excretion of bile pigments in the bile.

The effect upon the blood picture of the attack of hemolysis is of some interest. There is initially a leukopenia which is followed in several hours by a well-marked leukocytosis. Increased viscosity and lengthened coagulation time may accompany the period of leukopenia (Widal). The effect upon the red blood cell count will depend upon the severity of the attack. In some cases falls of over one million cells per cu mm have been observed. Rapid regeneration is the rule but in the cold season when attacks are frequent there is often a moderately severe secondary anemia.

The diagnosis of paroxysmal hemoglobinuria usually starts with the demonstration that the dark or bloody urine which has been noted by the patient owes its color to hemoglobin in solution and not to whole red blood cells. To establish this point a perfectly fresh specimen must be examined, the absence or rarity of erythrocytes proved, and the nature of the pigment spectroscopically.

determined. If intermittent hemoglobinuria is present the other features of the syndrome, hemoglobinemia, the induction of attacks by chilling the feet in cold water, the presence of the Donath-Landsteiner phenomenon, and the discovery of a history or of lesions or of serological tests indicative of syphilis, will serve to complete the diagnosis.

CASE REPORT

W B B, a white male, 30 years of age, by occupation a spinner of artificial silk, complained of recent attacks during which he passed bloody urine. He had been married for six years, his wife was living and apparently well. There had been one pregnancy which resulted in a still birth at full term. His family history was negative. He stated that prior to the recent illness his general health had been excellent. At the age of 18 he had had an attack of "three-day measles," at 19 epidemic parotitis and at 13 influenza. He at first denied any history of venereal disease but later let it be known that nine years before a positive Wassermann reaction had been found and that he had then received six injections of an arsenical at weekly intervals.

There had been no cardiorespiratory symptoms except for slight dyspnea on climbing a flight of stairs. His appetite, digestion and bowel function were normal. There was no history of icterus. There had been an occasional "stitch in the right side" while working (his occupation necessitating a half twist of the body). There had been no urinary symptoms prior to the recent illness. No joint symptoms, no disturbances in locomotion, nor had any abnormalities of the special senses been noted.

There was no history of bleeding, no epistaxis, hemoptysis, hematemesis or melena. The patient stated that he smoked moderately. He had not used alcoholic beverages for 12 years. There was no history of exposure to chemicals, nor of drug addiction nor of prolonged medication of any sort.

About November 1, 1933, the patient, having been exposed to cold weather for about three hours while hunting, became chilled and began to "quiver", at once he went to a house close by, where his temperature was taken and found to be 104° F. He stood before an open fire in this house for approximately three-quarters of an hour, feeling during this time perfectly normal. The first urine voided, about one hour later, was slightly tinted blood color, a second specimen one hour afterward was bright red, and the third, after about six hours, was clear. There were no abdominal cramps, pains, or discomfort, no icterus, pallor, flushing of the face, dizziness, tinnitus, headaches, nausea, vomiting, disturbances of vision, sweating or petechiae.

Following this initial attack, in the winter of 1933-34 there occurred five similar attacks. During the summer of 1934 no attacks were noted but about November 8, 1934, an attack again occurred. On this occasion he had been working on an automobile for about two hours on a cold day in a small garage without a stove. During the prodromal stage he felt that he was able to predict that the "urine would be bloody" because of his previous experiences, the feet and then the hands became rapidly and exceedingly cold, followed by a coarse generalized tremor and "nervousness". Upon entering the house to get warm, he noticed a fairly severe tinnitus and a feeling as if his head were swelling. The hemoglobinuria followed the same course as in previous seizures. Following this he came in for diagnosis.

Physical examination reveals a well nourished adult male, approximately 30 years of age, with slightly pale lips, but apparently in good health. Skin of normal color and texture. Head of normal contour, without softening, exostosis, or loss of hair. Tongue protrudes in the midline, without tremor, facial and masseter muscles are intact. Eyes pupils round and equal, react to light and in accommodation, extraocular movements normal, no nystagmus. No icterus. Ears hearing normal, slight

scarring of the right tympanic membrane. Nose symmetrical without discharge or deviation or perforation of the septum. Mouth no ulceration or scarring. Tongue normal. Upper teeth all extracted, others in good repair. Neck symmetrical, without retraction, muscle spasm, deviation or tug of trachea. Chest symmetrical, with normal respiratory excursion, lung fields are normal as to voice sounds, breath sounds, tactile fremitus, and percussion. Heart apex beat in the fifth interspace 8.5 cm to the left of the mid-sternal line, regular in rate and rhythm, without murmurs. Blood pressure 128 systolic and 80 diastolic. Abdomen symmetrical, painless at the level of the thorax. No muscle spasm, abnormal masses, or point tenderness. Costo-vertebral angle tenderness is absent. Genitalia no abnormal findings. Extremities symmetrical, without limitation of motion, scars, or tremors. Tendon reflexes present, equal and active. Babinski test causes plantar flexion of the great toes. Romberg is negative.

*Laboratory Examinations** Blood Hemoglobin 75 per cent, red blood cells 5.09 millions, white blood cells 8,650, smear normal. Wassermann and Kahn tests were positive (4 plus) colloidal gold 555554310000.

The Landsteiner phenomenon showed unmistakable hemolysis. A few cubic centimeters of the patient's blood were put in a test tube with a little citrate solution, and a normal control used. Both specimens were cooled to about 5° C for about 10 minutes and then warmed to 37° C. When the cells had settled out, the serum of the normal blood was a straw color and that of the patient's blood a wine color. Under the microscope the cells of the control were normal, while about one-third of those of the abnormal specimen were somewhat elongated with very slightly irregular outlines. Urine. A specimen taken when an attack was not imminent had a specific gravity of 1.012, and tests for albumin and sugar were negative. During an attack the benzidine reaction was strongly positive, and the red cells averaged less than two per low power field in a centrifuged specimen.

The Wassermann reaction on the blood of the patient's wife was strongly positive.

Course The patient was promptly placed on anti-syphilitic treatment. He received his first intravenous arsphenamine on December 21, 1934. Since that date there has been no recurrence of paroxysmal hemoglobinuria. During the ensuing 10 months the patient received 12 intravenous injections of neoarsphenamine, 12 intramuscular injections of bismarsen and interval oral administration of protoiodide of mercury. In late 1935 he was noted to be developing a noticeable increase in mental dullness and apathy, a forgetfulness in relation to misplaced articles of dress and ordinary use. His gait was uneven. A slight inequality of the pupils was found with diminished reaction to light. An observable slurring of test sentences was noted and an increase, bilateral and equal, of the biceps and knee reflexes. The spinal fluid Wassermann test was strongly positive. A diagnosis of paresis was made. Active treatment with mercury and arsphenamines was continued but without benefit. A course of hyperpyrexia of six weeks' duration had likewise no definite helpful effect.

SUMMARY

A case of paroxysmal hemoglobinuria is reported, occurring in a white male 30 years of age. Treatment of the patient's syphilitic infection led to prompt disappearance of the attacks of hemoglobinuria but the syphilitic infection progressed and outspoken general paresis appeared.

* We are indebted to Dr. Ivan H. Smith for the laboratory findings.

PERICARDITIS WITH EFFUSION COMPLICATING TULAREMIA*

By D D STOFER, A B M D , F A C P , *Kansas City, Missouri*

BECAUSE of the fact that tularemia is somewhat rare, its complications are not fully known. The purpose of this paper is to report the recovery of a case of tularemia in which pericarditis with effusion occurred as a complication. A search of the literature in the Surgeon General's Library and other available sources reveals but one other case of this kind. Pessin¹ (1936) reported a case of pericarditis with effusion complicating tularemia, which was diagnosed a few days before death of the patient and verified by autopsy findings. The clinical findings in his case as well as in this one were unquestionable as to the existence of a pericarditis with effusion.

CASE REPORT

The patient was a white woman, 29 years of age, married. Her husband and two children were living and well.

On November 8, 1936, her husband returned home with three rabbits which he had shot on a farm seven miles south of Belton, Missouri. She cleaned the rabbits that night. On the following Sunday, November 15, 1936, she noticed a small raised red area on the dorsum of her right index finger just back of the nail which she said itched considerably. The area became infected in appearance and began to ulcerate. Lymphatic glands in the epitrochlear region and axilla of the right arm commenced to swell markedly and become very painful. A day or so later she noticed a peculiar choky sensation in her throat, accompanied by nausea, profuse sweating at times, chills, fever and pleurisy-like pains in the left chest.

Physical Examination. At the first visit November 15, 1936, the patient's temperature was 103.2° F and her pulse 116. She appeared to be in a very excited and uncomfortable state, with difficulty in breathing because of the pleurisy-like pains in her left chest and very severe pains in the index finger of the right hand and up the arm into the axilla. Just back of the base of the finger nail of the right index finger there was an ulcerated area about 1 cm. in diameter with lifting of the edges. A large swollen and tender bunch of glands were evident in the epitrochlear region extending about one-third of the way up the arm from the elbow to the axilla. A group of swollen glands was also found in the axilla.

On further examination the following findings were noted. The tongue was furrowed, red and sore, there were a few small ulcerated areas along its edges. The examination of the heart was negative except for its rapid rate. A few moist râles were heard at the base of the left lung but there was no dullness to percussion. A very slight friction rub was present at the left base. The abdomen was slightly distended.

This clinical picture remained about the same, the temperature each day going as high as 102 to 103.8° F until November 29 when the patient's left chest became definitely dull to percussion over the entire lung area, some bronchial breathing appeared and more râles were evident. Hospitalization was deemed advisable.

The patient was admitted to St. Luke's Hospital on November 30. The tem-

* Received for publication August 2, 1937.

perature and pulse chart during her stay at the hospital from November 30, 1936 to February 7, 1937 is shown in figure 1

The results of laboratory examinations made during the patient's stay in the hospital were as follows

The agglutination test for *B tularensis* on the fifteenth day was negative, on the seventeenth day it was reported positive in all dilutions up to 1 640, and on the nineteenth day it was positive in dilutions up to 1 1280. A blood culture taken on December 2 was negative after 72 hours. On admission the white blood cell count was 11,800. Later counts up to January 30 varied between 8,300 and 12,600. The red blood cell count was 4,160,000 and the hemoglobin 89 per cent on admission, later counts showed no significant variation.

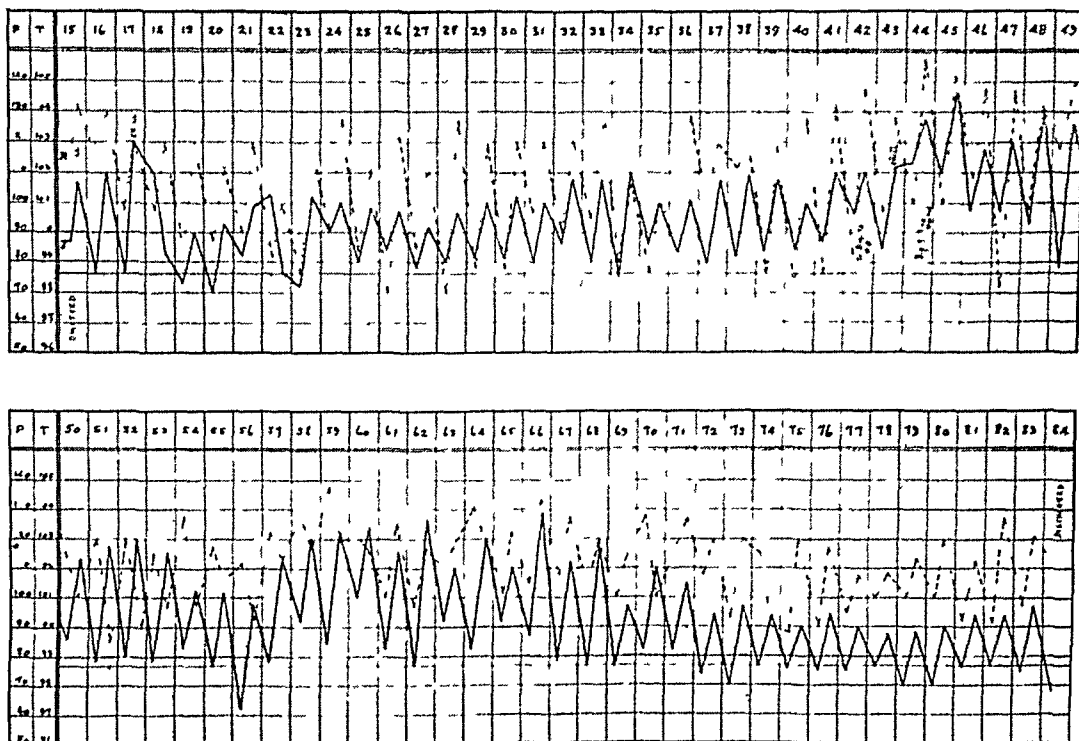


FIG 1 Temperature chart during the patient's stay in the hospital

The Wassermann and Kline tests were negative. Urinalysis on admission showed a faint trace of albumin and 10-12 red blood cells per high power field in the sediment.

On December 2, 1936 a roentgen-ray of her chest was taken (figure 2) which showed a definite pneumonitis of the left lung with some fluid at the left base. The heart shadow was normal in size and contour.

On December 6, 1936 there appeared on the right forefinger, hand and arm a large number of pustules which persisted for approximately two weeks. From the above date on to December 27, 1936 she complained of severe pain in her arm, chest, right side of neck and at times in the right side of her abdomen, accompanied by nausea and vomiting. No definite tenderness could be found over her appendix. A pelvic examination was negative.

December 27, 1936 she began to complain of tightness in her throat and of some

culty in breathing. A careful daily examination of the heart had disclosed nothing of importance until the above date when a slight increase of the area of cardiac dullness was noted. On December 28, 1936, the area of cardiac dullness was larger and by the following day was markedly enlarged. The heart sounds became very distant. The apex beat could not be felt.

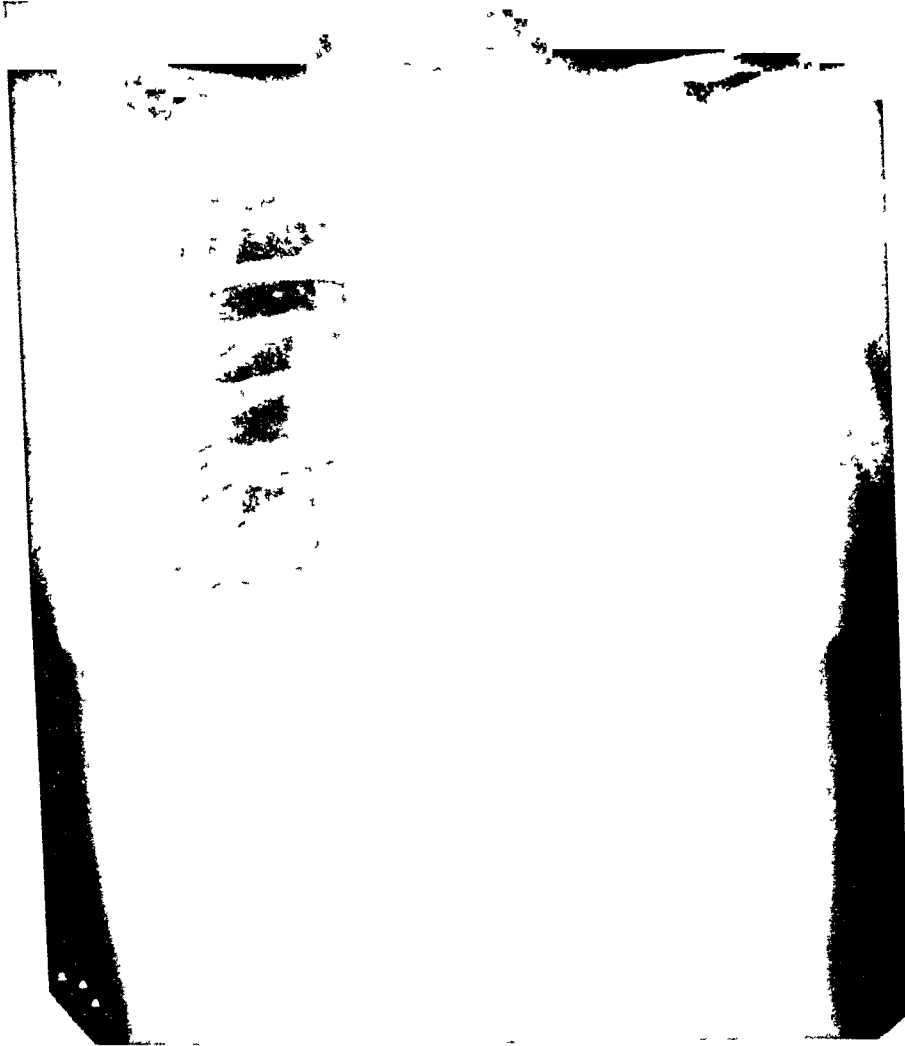


FIG 2 Roentgenogram during the active stage of the left pneumonitis and pleural effusion and before the development of clinical evidence of pericardial effusion (December 2, 1936)

A roentgen-ray of the chest (figure 3) on December 30 showed the pneumonic process in the left lung greatly improved but the heart shadow area enlarged from its previous greatest transverse diameter of 15.5 cm to 22 cm. There was a marked variation of density over the heart shadow area, particularly at the outer edges (not shown in the photographs as plainly as in the original film) suggesting a pericarditis with effusion. Another roentgen-ray on December 31 showed identical findings.

No pericardial friction rub was found until January 3, 1937, when it was very

pronounced. The rapid filling of the pericardial cavity probably accounted for the absence of the friction rub at first. The to and fro friction rub remained very constant day after day until January 12, 1937. On several days between January 3 and January 12 she was subject to sudden stabbing pains in her chest. On January 11 a definite and distinct pleural friction rub at the right base was noted which persisted for two days, and was intermittently observed thereafter until January 30, 1937 when all signs through her chest began rapidly to disappear. At no time during

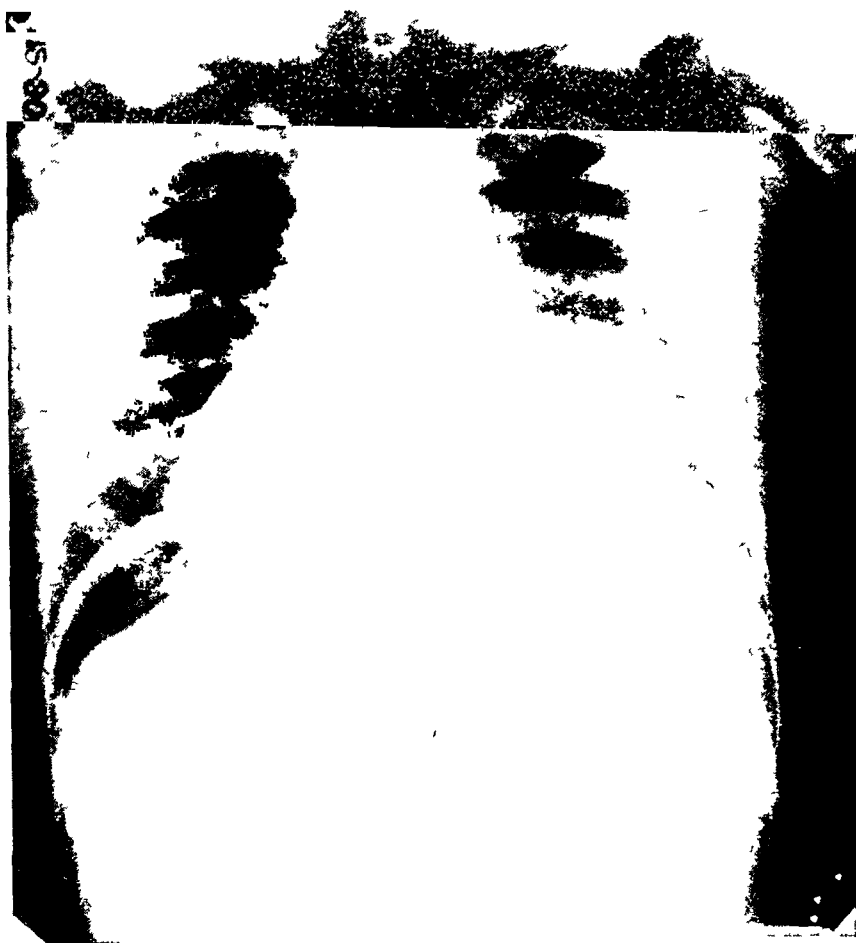


FIG 3 Roentgenogram showing pericardial effusion. Marked clearing of the left chest has occurred (December 30, 1936)

the course of the pericarditis with effusion was it deemed either necessary or advisable to tap the pericardial sac. The embarrassment of respirations experienced was at times considerable but never unbearable.

A roentgen-ray of the chest on January 15 showed some decrease in the heart shadow area. The lung fields appeared entirely clear at this time.

An electrocardiogram was taken on January 12 (figure 4). In the conventional

three leads P R I—0.15 sec, T_1 plateau type with slight convexity upward of R T_1 segment, T_2 and T_3 are diphasic, Q T—0.21. In the anterior chest leads (R A to front and L A to back) T_4 is diphasic and of low voltage, T_5 is diphasic and of low voltage but more upright than T_4 , Q_5 is smaller than normal.

Impression Impairment of coronary circulation leading to poor myocardial nutrition.

By February 3, 1937 very definite clinical improvement was evident. A roentgen-ray of the chest at this time (figure 5) showed a marked diminution of the area of the cardiac shadow. The lung fields were clear. The patient was dismissed from the hospital February 7, 1937 to go to her family's farm to recuperate. Upon dismissal she still had some enlargement and hardness of her epitrochlear glands. At

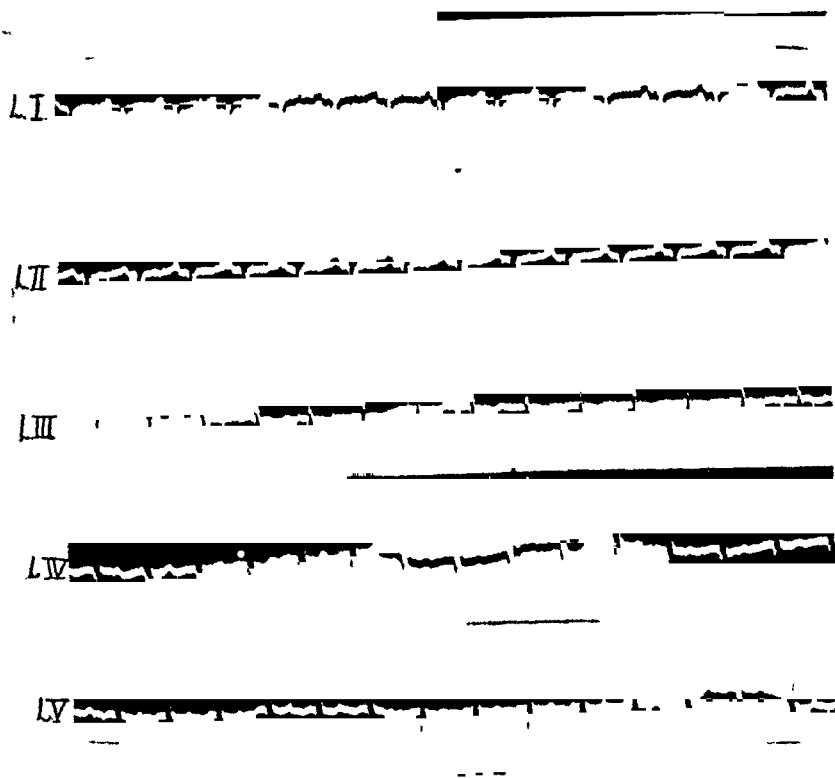


Fig 4 Electrocardiogram (January 12, 1937)

no time during the course of the disease did the glands suppurate enough to warrant incision and drainage or aspiration. The multiple pustules which had appeared during the third and fourth weeks of the disease were incised and drained to relieve pain.

Although some writers on the subject of tularemia report that the initial lesion disappears in a week or two after its inception it was observed in this case that the initial lesion on the finger lasted for over a month. The secondary pustules which developed on the arm about two weeks after the initial lesion appeared did not dry up until the same time that the primary focus disappeared.

The total duration of the illness in this case was 114 days. Following discharge the patient made a complete recovery and is at present well and leading a normal life.

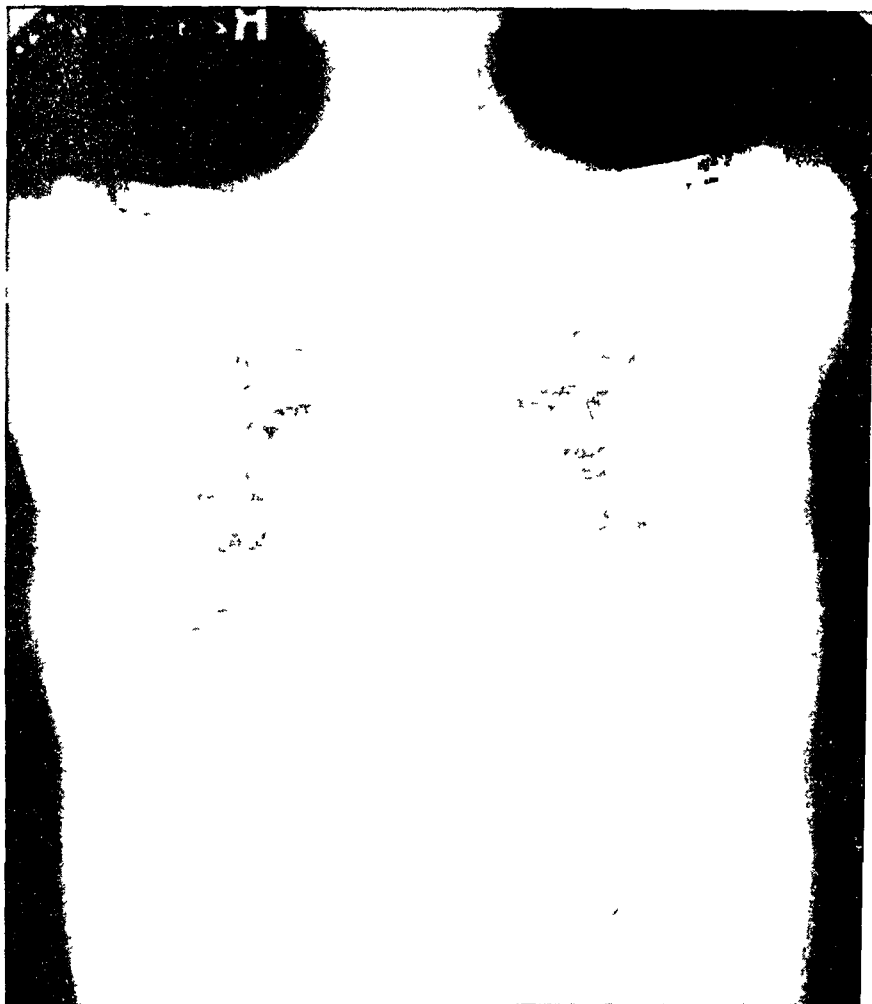


FIG 5 Roentgenogram showing reduction in area of heart shadow by February 3, 1937

SUMMARY

A case of tularemia of the ulcero-glandular type is reported in which pericarditis with effusion appeared as a complication. The patient made a complete recovery.

REFERENCE

1. PESSIN, S. B. Tularemic pneumonia, pericarditis and ulcerative stomatitis, *Arch Int Med*, 1936, lvi, 1125.

EDITORIAL

ERYTHROBLASTOSIS

The erythroblast is an immature form of red blood cell usually considered to be the next in sequence of development after the megaloblast. It contains a large nucleus and according to certain authors may contain nucleoli. According to others it never contains nucleoli and is incapable of mitotic division. It is evident that this is a matter of definition. The cytoplasm is basophilic and contains little or no hemoglobin. The diameter is variously given as from 8 micra to 25 micra. The smaller forms are certainly the more usual.

Erythroblasts are normally observed in the blood of new born infants during the first five days of life but thereafter they are normally found only in the red marrow where they constitute up to 5 per cent of the cells.

In anemias with rapid cell regeneration as after certain infections and in myelogenous leukemia, erythroblasts may appear temporarily in the blood and the younger the patient the more likely this is to occur. There are in addition, however, certain more or less specific types of anemia in infancy and childhood in which a very considerable number of such nucleated red cells are seen and it is to these that the term erythroblastic anemia has been applied. The specific features common to these anemias in addition to erythroblastemia are (1) the extramedullary proliferation of hematopoietic tissue and associated enlargement of the liver and spleen, (2) excessive blood destruction with varying grades of associated icterus, anemia and edema, (3) familial occurrence. The different types in this group are distinguished by their age of incidence and by their individual clinical features which often are very striking. Sufficient cases completely studied in life and as to their pathologic histology are not yet available to warrant any final classification. There is especially a lack of sufficient data for any final opinion on the hereditary factors in certain types of cases. Nevertheless a tentative description of the group is of interest.

Universal edema of the fetus, or congenital hydrops has long been known. The major portion of the course of this disease is run in utero and it results in the production of a non-viable infant or of a still birth. At birth the extreme whiteness of the infant suggests the severe anemia present. The vernix caseosa may be quite yellow. The patient is diopsical either in toto or as to the extremities. The placenta is edematous and enlarged often to several times its normal size. The enlargement of the spleen and liver are very marked. There is free fluid usually in all the body cavities.

If the child is living at birth respiration is usually irregular and gasping. The heart sounds are accompanied by hemic murmurs. The blood count shows a very severe anemia, frequently less than one million red blood cells.

per cubic millimeter being recorded. There are numerous erythroblasts and normoblasts the percentage of such nucleated forms often reaching 40 to 60 per cent of the total red cells. Immature white cells are likewise present.

The histological study of the organs shows striking increase in the erythropoietic activity not only in the bone marrow but in diffusely scattered foci in the spleen, liver, lymph glands, kidneys and numerous other glandular structures. Such foci are also present in the edematous placenta. Hellman and Hertig¹ believe that the pathologic picture of the large smooth edematous placenta of this condition is specific for the disease.

It has recently been shown that fetal hydrops can be diagnosed by the roentgen-ray in utero.² The edematous thickening of the scalp shows as a dark corona around the infant's skull. There is also thickening and increased density of the soft parts generally. Since the condition is incompatible with life and since it is familial, it is probably advisable to take roentgenograms of pregnant mothers who have previously given birth to erythroblastotic children. Such roentgen-rays are especially apt to show positive findings in the last two months of the pregnancy.

A recent study³ of the mode of inheritance of fetal hydrops has shown that in those families in which one or more cases of this condition have occurred there is also a high incidence of miscarriages and still births. A more careful pathological study of these products of conception might show that many were earlier forms of erythroblastosis. It seems probable that the occurrence of fetal hydrops in families is due to a dominant mutation.

Icterus gravis of the new born is another condition characterized by the presence of erythroblastic anemia, extramedullary hematopoiesis with enlargement of the liver and spleen and by a well marked tendency to familial incidence.^{4,5} At birth the vernix caseosa has usually been found to be of a golden yellow color. The infant is slightly icteric, the spleen and liver are already large and there are not infrequently small petechial hemorrhages. The jaundice tends to increase rapidly, the bleeding tendency becomes more marked with oozing of blood from the mouth, nose and in the urine and stools, and, unless relieved by treatment, death will usually occur within the first week. These cases show a severe anemia, the count frequently being below two million. There is a high percentage of nucleated red cells. The leukocytes are increased to around 25,000 in the average case, with evidences of marked immaturity among the myeloid cells. It has been noted

¹ HELLMAN, L. M., and HERTIG, A. T. The pathological changes in the placenta associated with erythroblastosis of the fetus, *Am J Path*, 1938, 14, no. 1.

² HELLMAN, L. M., and IRVING, F. C. The X-ray diagnosis of erythroblastosis, *Surg, Gynec and Obst*, 1938, LVII, 296-299.

³ MACCLIN, M. T. Erythroblastosis foetalis, a study of its mode of inheritance, *Am Jr Dis Children*, 1937, 11, 1245-1267.

⁴ CLIFFORD, S. H., and HERTIG, A. T. Erythroblastosis of the new born, *New England Jr Med*, 1932, CCXII, 105-113.

⁵ DIAMOND, L. K., BLACKFAN, K. D., and BATY, J. M. Erythroblastosis foetalis and its association with universal edema of the fetus, icterus gravis neonatorum and anemia of the new born, *Jr Pediat*, 1932, 1, 269-309.

in this condition that the red count may show a very rapid fall within a period of a relatively few hours, a phenomenon recalling the hemolytic crises observed in two other familial blood diseases, sickle cell anemia and congenital hemolytic jaundice. There may be slight edema present in the subcutaneous tissues of these cases. Transfusions appear to benefit many cases. Those patients in this group who survive frequently show severe grades of anemia for a long time after the icterus has disappeared. In some instances there has been evidence of persistent damage to the central nervous system. The later history of these cases deserves more intensive study.

The postmortem examination of cases of icterus gravis shows evidence of unusually active and widespread erythropoiesis in liver, spleen, kidneys and other organs. It is not perhaps usually of as embryonic a type as that seen in fetal hydrops. The enlarged liver shows vacuolization of many liver cells, bile casts in the bile ducts, hemosiderin pigment in the Kupffer cells. In some cases, the hematopoietic islands compress the liver columns, destroying liver cells. The nuclear structures of the brain may show intense icteric pigmentation. This condition described as "Kernicterus" is thought to be the cause of the persistent neurological defects.

Macklin in studying the inheritance of icterus gravis as exemplified in the published cases, found that in the families in which it occurs, a little over 50 per cent of the children are affected. This suggests that it is due to a dominant mutation. It is of interest that in a number of instances infants showing fetal hydrops and others showing icterus gravis have been born in the same family.

It is less clear whether the condition known as anemia of the new born, or hemolytic anemia of the new born, should be classed as another example of erythroblastosis. In the cases so designated neither icterus nor hydrops are prominent, though traces of either may be seen. A severe anemia is observed within a few days or weeks after birth. This anemia is usually accompanied by moderate evidences of immaturity among the red cells of the peripheral blood, but a true erythroblastemia is not a characteristic feature. Similarly, extramedullary hematopoiesis is not prominent in the pathological examinations of such cases. There is some evidence that anemia of the new born may occur in the same families in which fetal hydrops or icterus gravis have been observed.

A very interesting type of erythroblastosis is that first described by Cooley in Detroit in 1925 among American born children of Greek, Syrian or Italian parentage. Cooley and his colleagues in a number of papers define the essential features of this type of anemia now commonly known by his name. The onset of the condition is in infancy or in early childhood. There is a moderately severe anemia, with, as a rule, a low color index. The number of nucleated red cells is greatly increased, often to 5,000 per cmm. The majority of these are normoblasts, but 5 to 10 per cent may be erythroblasts. The spleen and liver are greatly enlarged, but the evidences of extramedullary hematopoiesis were found to be relatively scant in the

autopsied cases Evidence of chronic hemolysis in these cases exists in the form of a yellowish, muddy, skin pigmentation and an excess of urobilin in the urine There is usually a positive indirect Van den Bergh reaction and an increased icterus index There is a distinct familial character to the disease, as well as a racial distribution The striking feature of this chronic familial type of anemia is that it exhibits bone changes similar to those seen in certain cases of sickle cell anemia and familial hemolytic jaundice These bone alterations consist of irregular lacunar areas of osteoporosis, most commonly seen in the pelvic bones, femurs, and the metatarsals and metacarpals In addition, there are striking vertical striations in the enlarged diploe of the skull These changes may also affect the malar bones The color of the skin and the changes in the contour of the face join in giving to these patients a rather marked mongoloid appearance The course of Cooley's anemia is usually fatal, death occurring before puberty

Until very recently the total number of cases reported of this disease did not exceed sixty The great majority had been observed in the United States An important publication has just appeared, based upon the studies of Caminopetros⁶ in Greece The author has observed 36 cases in the course of the last three years Since certain of these were refugees from Asia Minor, he feels that the disease deserves investigation among all the peoples of the Near East Caminopetros believes that a definitely increased resistance of the red blood cell to salt solutions is an essential feature in Cooley's anemia Moreover, he feels that he has shown that this characteristic of the disease is frequently present in members of the families of patients who do not themselves show any manifest anemia He is inclined to feel, that since the condition may be transmitted by apparently normal adults, there is a real possibility that the disease may increase in frequency He points out that radiologic examinations of the recovered skulls of members of the vanished Maya Indian race have shown severe osteoporotic lesions quite similar to those seen in the erythroblastic anemia described by Cooley This raises the question, he feels, as to whether a familial anemia fatal before puberty may not endanger the existence of a race

In this brief summary the many diagnostic difficulties which arise in connection with the separation of the above described types from conditions nearly resembling them have not been discussed Much further study of these types and of closely similar conditions will be necessary before the true significance of the resemblances between the different types of erythroblastosis can be finally determined

⁶ CAMINOPETROS, J L'anemie erythroblastique infantile, *Ann d Med*, 1938, xliii, 27-61 and 104-125

REVIEWS

How Ancient Healing Governs Modern Therapeutics By KLEANTHES A. LIGEROS, M.D., Ph.D. Illustrated xx + 523 pages Index G. P. Putnam's Sons, New York and London 1937 Price, \$10.00

Dr. Ligeros apparently has taken up a twofold task. The first is to show that medicine has advanced very slowly, and in some respects not at all, since the days of ancient Greece. His second, and major thesis, is to demonstrate that "Chiropractic" or "rachiopathy" was an important branch of treatment in the Hippocratic school, and is now, in spite of the reluctance of the medical profession to approve it, coming into its own as a modern therapeutic method.

Several quotations might be cited. On page 48 "Among the systems to be thus reborn is rachiopathy and rachiopathy, rediscovered in America forty years ago as chiropractic, and advanced since that time as a new science and art. Its efficacy and scientific value have been verified and confirmed by modern research as well as by the findings of the ancient Greeks." Page 81 "Taking into consideration the conflicting and chaotic condition of today and the untold and endless theories propagated so far—which change before they can be reasonably discussed—and the advances in medicine relative to the cause of disease, it is not difficult to prove that perhaps the ancients were better off and nearer the truth than we are." Page 82 "Evidently the new theories of the cause of disease (such as the germ theory of Pasteur) have not yet solved the problem which keeps the medical world divided and disdainful. Undoubtedly, the germ theory of the cause of disease still remains a source of academic discussion and a question to be answered." "In the sphere of actual technique, the modern physician is left astonished and dumbfounded, not being able to equal or meet his predecessor half way." Page 93 "Sanitation, hygiene, and dietetics were developed so adequately from the time of Hippocrates that even today science has not added anything of great importance to them, particularly to the last named." Many more such statements could be quoted, but these passages give a fairly accurate picture of the general tone of the book.

Much space is devoted to the Homeric period. Most of this is irrelevant, though interesting. In describing the knowledge of pharmacy possessed by the Homeric Greeks, one author states that Circe, the enchantress, knew a number of effective drugs with which she transformed Ulysses' crew into swine, the modern pharmacologist has certainly not succeeded in performing this feat! Dr. Ligeros makes no distinction between legend and historic fact, and, if the reader's only acquaintance with Greek culture was through the present volume, his opinion would certainly be distorted.

Two appendices are included. One is titled "Chirurgy in Ancient and Modern Times," and the other "An Historical Acknowledgment on the Discovery of Modern Rachiotherapeutics." The second appendix, as suggested by the title, takes up the history of modern "Chiropractic." D. D. Palmer, the founder, is quoted extensively from his book "The Science, Art and Philosophy of Chiropractic." The first appendix, also, is largely devoted to Chiropractic methods, and opinions of Goldthwait, Still, and others are quoted as approving the Chiropractic method. The author seems unable to distinguish between true disease of the spine, and the so-called subluxations that, according to the "Chiropractic School" are responsible for all human ills.

This book is not recommended for the physician or medical student, but it should certainly be in every Chiropractic's library.

T N C

Artificial Fever Produced by Physical Means Its Development and Application By CLARENCE A. NEYMANN, A B, M D, F R S M 294 pages Charles C Thomas, Springfield and Baltimore 1937 Price, \$6 00

The book is well planned, nicely illustrated and very well printed, though the print is rather small. It is divided into 15 chapters including The Basic Theories and Principles, History, Physiology (two chapters), Technic of Electropyræxia, Dementia Paralytica, Syphilis of the Central Nervous System, Primary and Secondary Syphilis, Multiple Sclerosis, Chorea Minor, Arthritis, Gonorrhoea, Asthma, Other Diseases, Dreams and Facts. There is a preface, a subject and an author index and an extensive bibliography of 556 references.

The author's chief interests are in psychiatry and his material was drawn mainly from that field. He was the first to produce artificial fever for therapeutic purposes by means of diathermy, a fact that the reader is never for a moment allowed to forget. This insistence somewhat mars the book, nevertheless, it is a valuable exposition of a method of therapy that is now exciting widespread interest.

T P S

Digestive Tract Pain, Diagnosis and Treatment, Experimental Observations By CHESTER M. JONES The Macmillan Co., New York, 1938 152 pages Price, \$2 50

Over a period of fourteen years the writer has been interested in the subject of pain arising from the viscera of the digestive canal. Long series of normal individuals and of patients have been studied as to the nature and site of their painful sensations when a small balloon was inflated, causing distention at a definite level in the tract. In general, the results are confirmatory of those obtained by others. The presentation of these experiments yields an interesting review of the subject. The practical deductions which may be drawn from such knowledge are indicated in the latter half of the book which is given up to case protocols. It is a book which will stimulate a more thoughtful consideration of the diagnostic value of pain.

M C P

The Culture of Organs By ALEXIS CARREL and CHARLES A. LINDBERGH Paul B Hoeber, Inc., New York 1938 221 pages Price, \$4 50

The culture of organs in vitro could not be successfully achieved until many difficulties had been overcome. A medium must be perfused through an organ under a pulsatile pressure. This medium, as well as the organ, must remain sterile. The fluid must be kept suitably oxygenated, free of particles and exactly adjusted as to temperature, osmotic pressure, pH and maximum and minimum pressures. In 1931 Lindbergh devised an apparatus which could be kept sterile but it failed in other particulars. It was only in 1934 that the first form of the successful pump was obtained and the following year when the organ chamber was perfected. Successful perfusion of living organs for periods of weeks ensued. Since 1935 numerous experiments have been carried out with this technic by the senior author and others, exploring the effects upon the structure and function of living organs of induced variations in their milieu. It is obvious that by this means a series of hitherto inaccessible problems may be attacked.

The description of the philosophy of the method is in interesting contrast to the clear and precise instructions for the construction and operation of the apparatus. The conjunction of separate abilities was needed to make available this valuable new tool for biological research.

M C P

Tuberculosis Among Children and Young Adults By J ARTHUR MYERS 2nd Edition 401 pages Chas C Thomas, Springfield, Ill, and Baltimore, Md 1938 Price, \$4 50

The author has devoted the greater part of this book to a description of the nature of the first infection type and of the reinfection type of tuberculosis in infants, children and young adults, and particularly to discussion of how these young individuals acquire these lesions and how they may spread them. He tries hard to impart to the reader his own zeal for stamping out tuberculosis. Since he has had an unusually full experience in tuberculosis detection and in the working out of preventive measures his book is very interesting and valuable from these points of view. It is, however, touched with the optimism of the crusader. The author seems a bit uncritical and shows little desire to weigh and evaluate contrary opinions.

There is a lack of clinical description of the disease. Indeed our interest in the clinical aspects is rather rebuffed and we are led firmly back to periodic tuberculin tests and routine roentgen-rays of positive reactors.

On the whole this is a valuable book on the pathogenesis and on the prevention of tuberculosis in the earlier years of life but the practising physician will need another volume on the clinical details to attain a balanced view of the subject.

M C P

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library are gratefully acknowledged

Rear Admiral Charles S Butler, F A C P , M C , U S Navy—1 reprint,
Dr Julius P Dworetzky, F A C P , Liberty, N Y—2 reprints,
Dr Herbert R Edwards (Associate), New York, N Y—3 reprints,
Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,
Dr Jacob Gutman, F A C P , Brooklyn, N Y—Third, Second Series, Supplement to
"Gutman's Modern Drug Encyclopedia",
Dr Lynn T Hall, F A C P , Omaha, Nebr—1 reprint,
Dr Irving R Juster (Associate), Glens Falls, N Y—3 reprints,
Dr Albert Benjamin McCreary (Associate), Jacksonville, Fla—1 reprint,
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Dr Aaron E Parsonnet, F A C P , Newark, N J—1 reprint,
Dr Kenneth Phillips, F A C P , Miami, Fla—2 reprints,
Dr Edwin T Thorsness, F A C P , Denver, Colo—5 reprints,
Dr Emil G Vrtiak (Associate), Chicago, Ill—2 reprints

NEW LIFE MEMBER

Dr George Bruce Lemmon, F A C P , Springfield, Mo , has lately become a Life Member of the American College of Physicians

AMERICAN BOARD OF INTERNAL MEDICINE

Written examinations for certification by the American Board of Internal Medicine will be held in various parts of the United States on Monday, October 17, 1938, and on Monday, February 20, 1939

Formal application must be received by the Secretary before September 15, 1938, for the October, 1938, examination, and on or before January 1, 1939, for the February, 1939, examination

Application forms may be obtained from William S Middleton, M D , Secretary-Treasurer, 1301 University Ave , Madison, Wis

At the annual meeting of the Santa Clara County Tuberculosis Association held at San Jose, Calif , in June, 1938, the guest speaker was Dr Francis M Pottenger, Sr , F A C P , Monrovia, Calif

Dr C Kelly Canelo, F A C P , San Jose, Calif , was elected President of the Santa Clara County Tuberculosis Association for the coming year

The Committee of Physicians held its first annual meeting at Cornell University Medical College, New York City, July 21 Dr Richard M Smith of Harvard Medical School was elected chairman Dr Hugh Cabot, Rochester, Minn , and Dr William J Kerr, F A C P , San Francisco, were elected vice chairmen Dr Russell L Cecil, F A C P , New York, the retiring chairman, was elected honorary chairman,

and Dr John P Peters, New Haven, was reelected secretary The deliberations of the Committee were closed to the press

Dr Carleton B Peirce, F A C P, for a number of years Associate Professor of Roentgenology at the University of Michigan Medical School and the University Hospital, Ann Arbor, has received the appointment as Director of the Department of Radiology at the Royal Victoria Hospital Montreal, succeeding Dr A Howard Pirie

At the invitation of the Vitamin Advisory Board of the U S Pharmacopoeia, a notable gathering of vitamin experts, some ninety in number, took place in New York on July 22 and 23 The discussion covered tests and bio-assays for new vitamin preparations to be introduced into the Pharmacopoeia Among other things, it was recommended that solutions of three strengths of vitamins A and D be prepared in corn or cottonseed oil to eliminate the fishy taste and odor of cod liver oil, and that a preparation of vitamin A be furnished without D As President of the U S Pharmacopoeia Convention, Dr Walter A Bastedo, F A C P, New York, took part in the deliberations

Dr Anita M Muhl, F A C P, San Diego, Calif, has accepted a call for three years to lecture at the University of Melbourne, Australia

Dr William J Mallory, F A C P, President of the Medical Society of the District of Columbia, and Dr Frederick A Willius, F A C P, of the Mayo Clinic, Rochester, Minn, will be guest speakers on the program of the Sixty-ninth Annual Session of the Medical Society of Virginia at Danville, October 4, 5 and 6, their respective subjects being, "The Diagnostic Value of the Clinical Aspects of Digestive Disease" and "The Effects of Protracted and Recurrent Congestive Heart Failure on the Liver"

Round Table conferences will be a feature of this Society's meeting this year, and the following members of the College are among leaders

Dr Walter B Martin, F A C P, Norfolk, and Dr David P Scott, F A C P, Lynchburg—Acute Respiratory Diseases,
Dr Oscar Swineford (Associate), University—Allergic Diseases,
Dr A B Hodges, F A C P, Norfolk, and Dr F H Smith, F A C P, Abingdon—Etiology and Treatment of Indigestion,
Dr George B Lawson, F A C P, Roanoke—The Vitamins

Dr B R Kirklin, F A C P, Head of the Section on Roentgenology at the Mayo Clinic and Professor and Director of the Division of Radiology, Mayo Foundation, will act as the leader of a Round Table conference on Radiology before the annual meeting of the Virginia Radiological Society in October Dr Kirklin is a past president of the American Roentgen Ray Society and at present chairman of the Section on Radiology of the American Medical Association

The American Medical Association will meet in St Louis in 1939, New York in 1940 and Cleveland in 1941 Dr Rock Sleyster, F A C P , Wauwatosa, Wis , Governor of the College for Wisconsin, is now President-Elect

Dr Beverley R Tucker, F A C P , Richmond, Va , gave a series of six lectures in neuropsychiatry before the Florida State Medical Association at Daytona Beach during June

With Surgeon General Thomas Parran, F A C P , acting as chairman, a meeting of laboratory workers from the entire country and physicians and health officers interested in the control of syphilis will be held in Hot Springs, Ark , October 21 to 22, under the auspices of the Committee on Evaluation of Serodiagnostic Tests for Syphilis of the United States Public Health Service

Dr Oscar B Hunter, F A C P , Washington, D C , has been elected President, and Dr J Burton Glenn, F A C P , Washington, D C , has been elected Treasurer of the George Washington University Medical Society

Dr Earl B McKinley, F A C P , Washington, was elected President of the American Association of Pathologists and Bacteriologists at its last meeting At the time this news note is prepared, we note with grave concern that Dr McKinley was a passenger on the Hawaii Clipper, which apparently has been lost in the Pacific on July 28

Dr Walter L Treadway, F A C P , Assistant Surgeon General of the U S Public Health Service, Washington, has been made Medical Officer in Charge of the Federal Narcotic Farm at Lexington, Ky , succeeding Dr Lawrence Kolb, F A C P , who has been transferred to Washington to become Assistant Surgeon General

Dr C R Bennett, F A C P , Eufaula, Ala , and Dr Seale Harris, F A C P , Birmingham, Ala , have been elected Second Vice President and Member of the Council, respectively, of the Chattahoochee Valley Medical Association

Dr Edgar Hull, F A C P , has been elected Vice President of the Faculty Club of Louisiana State University School of Medicine, New Orleans

Dr Victor F Cullen, F A C P , State Sanatorium, has been elected a Vice President of the Medical and Chirurgical Faculty of Maryland

Dr Leon S Lippincott, F A C P , Vicksburg, Miss , is Secretary of the Hospital Service Corporation of Mississippi

Dr Frank D Gorham, F A C P, and Dr L P Gay, F A C P, both of St Louis, have been elected President and Treasurer, respectively, of the Missouri Chapter for the Advancement of Gastroenterology

Dr D W Carter F A C P, Dallas, Dr W W Bondurant (Associate), San Antonio, and Dr V E Schulze, F A C P, San Angelo, have been elected President, Vice President and Secretary, respectively, of the Texas Railway Surgeons Association

Dr William B Newcomb F A C P, Norfolk, has been elected President of the Norfolk County (Va) Medical Society

Dr Myrtelle M Canavan, F A C P, Curator of the Warren Anatomical Museum at Harvard, is a member of the editorial board of the American Medico-Legal Association, with headquarters in Boston Dr Frederick C Warnshuis of San Francisco, formerly secretary of the California Medical Association, has accepted the presidency and editorship-in-chief of this organization

Dr Julius H Hess, F A C P, and Dr Robert A Black, F A C P, both of Chicago, were among the lecturers in a graduate course in obstetrics and pediatrics conducted at Research and Educational Hospital, Chicago, during July and August The course was given under the auspices of the University of Illinois

Dr Elmer L Sevringhaus, F A C P, Madison, Wis, Dr William D Sansum, F A C P, Santa Barbara, Calif, and Dr Lawrence Reynolds, F A C P, Detroit, Mich, will be guest speakers on the program of the Sixteenth Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society, October 3 to 6

Dr Edgar A Hines, F A C P, Seneca, S C, was honored at a recent meeting of the South Carolina Medical Association, at which a silver tray, pitcher and goblets were presented to him in recognition of his long service as Secretary and Editor of the journal of that Association Dr Hines has been Secretary since 1909 and Editor of the Journal since 1912

Dr Henry Chesley Bush, F A C P, Livermore, Calif, has been elected President of the National Tuberculosis Association, Dr Frederick T Lord, F A C P, Boston, and Dr Paul P McCain, F A C P, Sanatorium, N C, were elected vice presidents

Dr Ralph Pemberton, F A C P, Philadelphia, has been elected President of the International Congress on Rheumatism The next meeting of this body will be held in New York during June, 1940

Dr Cecil O Lorio, F A C P, Baton Rouge, La, gave a refresher course on pediatrics in Marksville, La, June 13 to 17, under the auspices of the committees on medical education and pediatric courses of the State Medical Society and the Bureau of Parish Health Administration and the Division of Maternal and Child Health of the State Board of Health

Dr Thomas B Magath, F A C P, Rochester, Minn, is President of the American Society of Clinical Pathologists

In recognition of his many years of service, Dr William H Marshall, F A C P, Flint, Mich, has been made Director Emeritus of the Department of Internal Medicine at Hurley Hospital

Dr Benjamin B Souster, F A C P, St Paul, has been elected Secretary of the Minnesota State Medical Association

Dr O H Perry Pepper, F A C P, Professor of Medicine in the University of Pennsylvania School of Medicine, was the recipient of the honorary degree of Doctor of Science from Lafayette College, Easton, Pa, at its recent commencement

Dr Thomas D Cunningham, F A C P, Denver, Colo, and Dr Joseph C Kamp, F A C P, Casper, Wyo, addressed the thirty-fifth annual meeting of the Wyoming State Medical Society at Laramie, during August, on "The Treatment of Severe Asthmatics" and "Use and Abuse of Sulfanilamide," respectively

Dr David P Barr, F A C P, St Louis, is President of the Association for the Study of Internal Secretions The next meeting of this Association will be held in St Louis during the spring of 1939

Dr Oliver P Kimball, F A C P, Cleveland, Dr James B Collip, F A C P, Montreal, Dr Henry J John, F A C P, Cleveland, and Dr David Marine, F A C P, New York City, were speakers on the program of the International Goiter Conference held in Washington, D C, September 12 to 14 The American Association for the Study of Goiter and the Medical Society of the District of Columbia acted as hosts

Dr Thomas Parran, F A C P, Surgeon General of the U S Public Health Service, was one of the speakers at the dedication of the Hall of Science of the Golden Gate International Exposition at San Francisco during June

Dr Charles P Cake (Associate) has been appointed Chief Medical Officer in Tuberculosis at the Gallinger Hospital, Washington, D C

OBITUARY

DR EARL BALDWIN MCKINLEY

Dr Earl Baldwin McKinley (F A C P 1924), Dean of the Medical School, Professor of Bacteriology and Director of Medical Research, George Washington University was one of the fifteen persons aboard the 26-ton Hawaiian Clipper which disappeared on July 28, 1938, under most mysterious circumstances en route from Guam to Manila. A thorough systematic search in which all branches of the military forces of the United States stationed in the Philippines took part, assisted by the Commonwealth of the Philippines and Japan, failed to disclose a single vestige of the superliner or its occupants other than a mixture of gasoline and oil on the surface of the water near the zone from which radio communication was last received. There seems to be no doubt but that the transport plunged into the Pacific Ocean at one of its deepest points under conditions the nature of which will probably never be revealed.

Earl McKinley was born at Emporia, Kansas, on September 28, 1894. He prepared for college at the Newton High School, Newton, Kansas, and entered the University of Michigan on the combined curriculum in letters and medicine September 27, 1912. He received the degree of A B in 1916. His work in the medical school was interrupted by the world war. He entered the service May 7, 1917, going directly to the Reserve Officers Training Camp at Fort Sheridan, Illinois, and was discharged August 8, 1919, with the rank of first lieutenant. He was with the Rainbow Division overseas and saw action in the Marne offensive of July and August 1918. In September, 1919, he returned to the University to complete the medical course and in 1922 was granted the degree of M D. During this period he served as an assistant in bacteriology and was an instructor in physiological chemistry. In these capacities he came into direct contact with Dr F G Novy, whose stimulating influence he frequently acknowledged and whose advice and aid he constantly sought.

Shortly after completing the required program of study in medicine and before entering on an internship for which he had qualified, Dr McKinley was appointed assistant professor of bacteriology and pathology at Baylor University, Dallas, Texas. While at Baylor he investigated some of the fundamental aspects of the d'Herelle phenomenon and the clinical application of the bacteriophage in the treatment of a number of disorders, especially bacillary dysentery. These experiences crystallized his thoughts and he realized his interests were in research rather than the practice of medicine. Therefore, in the spring of 1924, although he had been advanced to a full professorship and head of the department of bacteriology, he applied for and was granted a National Research Council Fellowship in the medical sciences. He arrived with his family in Brussels in August, 1924, and at once went to work under Professor Jules Bordet at the Pasteur In-

stitute This contact with foreign workers which extended over a year was of inestimable value and resulted in the publication of four papers on certain aspects of immunity

While in residence abroad he accepted an appointment as assistant professor of bacteriology in the College of Physicians and Surgeons of Columbia University and arrived in New York in the fall of 1925 to assume his duties For two years he shouldered his full share of the regular instructing load and developed a special course in the filterable viruses His renewed interest in the ultraviruses was the natural outgrowth of his early experiences with the bacteriophage and now broadened to encompass such diseases as poliomyelitis and encephalitis lethargica His services were promptly recognized by an advancement in rank to that of associate professor of bacteriology An inherent faculty for organizing and administration led to his selection in the establishment of the division of bacteriology at the new School of Tropical Medicine in Puerto Rico and he spent several weeks in this capacity in Puerto Rico in September 1926 It was during this activity that he became imbued with the necessity for a greater breadth of experience Accordingly, he relinquished his connections in New York and arrived in Manila early in June, 1927 to take the position as field director with the International Health Division of the Rockefeller Foundation He was charged with the duty of reorganizing the public health laboratory service in the Bureau of Science cooperating with the Department of Health of the insular government This undertaking was satisfactorily consummated within the year In the meantime, a new School of Hygiene and Sanitation was established in affiliation with the medical school of the University of the Philippines, and McKinley taught bacteriology there for one trimester The demands of either of these assignments were enough to keep an ordinary individual occupied, but he found time to assemble the data for and to write a monograph of 412 papers on "Filterable Viruses and Rickettsia Diseases"

Having accomplished the task for which he was originally sent to the Philippines and fearing that the projected plans of the Foundation would involve him in endless administrative detail and thus submerge experimental work, he was quite willing to rejoin his old department at Columbia when the call came in the spring of '28 He was appointed professor of bacteriology and director of the School of Tropical Medicine of the University of Puerto Rico under the auspices of Columbia University Again he moved his family half way around the world and in September 1928 took up his duties in San Juan shortly after the island had experienced one of its most devastating storms For three years he devoted himself unsparingly to the development of the School of Tropical Medicine and the Hospital and their relationship to the local medical problems and medical profession His sponsoring of the establishment of the *Puerto Rico Journal of Public Health and Tropical Medicine* on a quarterly basis which has

served as the principal medium for publications from the school was an outstanding achievement. This journal has appeared regularly and has gained an enviable reputation in its particular field. Administrative duties in this new assignment were very demanding but odd moments were found for the bacteriological investigation of a number of local diseases.

The summer of 1930 was spent in residence at the University of Chicago, where, in the capacity of a visiting professor, he presented a special course on the ultraviruses. At this time he realized that his two children born while he was still a medical student in Ann Arbor were rapidly approaching the age where the demands of their education could be satisfied only in the States. Accordingly, they were placed in school here, and he and Mrs. McKinley returned to San Juan in the fall. This break in the home life he appreciated was only the beginning of a long period away from the children and he concluded that under these circumstances his connections in Puerto Rico could not be permanent. In the winter of 1931 in collaboration with the writer, studies on leprosy were begun at the School of Tropical Medicine. Attempts were made to cultivate the causative agent of this disease and to transmit the malady to laboratory animals. The results of these experiments were published, and in 1937 McKinley spent his sabbatical leave in the Philippines confirming and extending these investigations. He had with him on the flying boat a number of specially prepared substances which were to be used in the skin-testing of patients with leprosy in Manila.

In September 1931, he accepted the Deanship of the Medical School of George Washington University and took up his abode in Washington. In this new environment the prodigious energy of the man was unleashed. It would be impossible to enumerate the ramification of his activities or his accomplishments over the past seven years. He threw himself unstintingly into the task of reorganizing the staff and physical plant of the medical school. Under his direction this proceeded with a minimum of delay and conflict, and the present condition of the institution is a monument to his efforts. He was a born leader, and in Washington the multiplicity of scientific organizations with which he promptly affiliated responded to the stimulus of his personality. His proved ability as an administrator was responsible for his appointment to innumerable committees and election to executive positions in a large number of organizations. At the time of his disappearance, to mention only a few of his affiliations, he was president of the Society of Pathologists and Bacteriologists, executive secretary of the American Foundation of Tropical Medicine which with the Academy of Tropical Medicine owes its existence to his indefatigable interest in tropical diseases, and a member of the executive committee of the American Association for the Advancement of Science. The services of Dr. McKinley in this latter organization, first as Secretary of Section N (medical) and then as a member of the executive committee were outstanding and are worthy of special acclaim. He gave freely of his time in the preparation of the

programs of the medical section and his contributions to the deliberations of the executive committee were significant and far reaching

One might conclude that the demands of the aforementioned interests would preclude active participation in research, but such was not the case. He continued his investigations of the ultraviruses and published a number of papers in this field, as well as on leprosy. In addition, under the sponsorship of the National Research Council he conducted a survey of tropical medicine, spending considerable time abroad in the gathering of the data. This material was published in a monograph entitled "A Geography of Disease" and is recognized as a valuable contribution. On the tragic voyage he was extending this study by taking samples of the microbic content of the air at various points over the Pacific which were to be later identified in an effort to unravel the enigma of the trans-oceanic spread of pathogenic organisms.

In 1917, he married a classmate, Leola Edna Royce of Saulte Ste Marie, Michigan, who survives him. Two children were born to them, Janet and Royce, both of whom are in college. Mrs. McKinley, although never robust, was ever his constant companion and usually accompanied him on all of his trips. Their hospitable home was open to a host of loving friends. His untimely death at the height of a brilliant career has removed prematurely one who had given his full share, but who had still much to give. His loyalty, friendship and generous support of all worthy enterprises have enriched the world.

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NUTRITIONAL DEFICIENCY

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NUTRITION is the process of using substances derived from food for growth and for maintaining the integrity of the living organism. It consists, as McCarrison¹ has stated, in the taking into the body proper and in the assimilation there of materials with which the tissues of the body are built up, their waste repaired and their deterioration prevented. The materials affecting the function of nutrition are oxygen, water, protein derivatives, fats, carbohydrates, mineral elements, and vitamins, among which may be included material effective in pernicious anemia. Nutritional deficiency may arise from insufficient energy production as a result of an inadequate caloric intake, but it is protein, vitamin and mineral deficiency that commands our attention today.

"Deficiency disease" is a term which by custom was applied first to conditions where the causal factor was deficiency of vitamins in food, and more recently has been used to include disorders arising from lack of minerals and other nutritional factors. Nutritional deficiency disease is apt to be still thought of as arising only from a dietary defect. Nutrition, however, depends upon not only what man decides to eat but on numerous other factors such as the digestion, absorption, and proper utilization of sufficient amounts of the 36 or more substances required for health. Vitamin and mineral deficiency disease can be profitably thought of as due to the failure of consumption or lack of utilization or loss from the body of these essential factors. The nutritional essentials, the lack of which causes deficiency disease, serve as chemical links in the chain of normal metabolism and can not be manufactured by the body from purified fats, carbohydrates and proteins. It is natural that a defect of diet should be considered the cause of vitamin deficiency. However, on reflection it is at once apparent

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that the more proximate factor is the exhaustion or loss of the vitamin by the body through natural metabolic processes. A defective diet may be the cause of the disturbance but only through failure to replace the defect within the body. Thus, defective food can not be considered the cause of deficiency disease in quite the same sense, for example, that infected food is recognized as responsible for typhoid fever or botulism.

THE EFFECT OF THE UTILIZATION OF ENERGY

The effect of the utilization of energy on the production of vitamin deficiency is significant. In general terms the greater the chemical activity the more rapid is the depletion of substances in the bodily environment, the lack of which is responsible for nutritional deficiency disease. Thus, although in complete starvation the vitamin intake is nil, starvation is seldom associated with signs of vitamin deficiencies, in part perhaps because the metabolism is depressed and in part because there is insufficient time for the exhaustion of the vitamin stores before death ensues from general inanition. On the contrary, when the caloric content of the diet is high or the total energy expended is high and the vitamin intake is low, vitamin deficiency in many instances develops relatively easily and rapidly. The ease with which a variety of vitamin deficiencies develops in individuals who chronically imbibe large amounts of alcohol and who are very apt to select a poor diet, serves as a striking example, although very many calories may actually be derived from distilled spirits they supply none of the other nutritional essentials.

That exhaustion of the supply of nutritional factors in the body is the essential basis of deficiency disease is also indicated by the fact that such disorders are particularly apt to develop at a time in life when the demands for these factors are greatest, namely in infancy and childhood, owing to growth, and in pregnancy and the puerperium when the physiological strain of child-bearing and lactation requires dietary factors to be from 10 to over 100 per cent greater than the standard requirements for normal women.

The effect of an increased expenditure of energy on the precipitation of deficiency disease is to be observed where scurvy and beri-beri are endemic because these conditions are prone to develop in individuals undertaking the greatest amount of physical exertion. It was recognized by navigators of the seventeenth century that sailors undertaking the hardest labor were affected by scurvy before the men occupied with duties calling for little physical strain. Pathological disturbances such as thyrotoxicosis leading to accelerated oxidation processes may also affect the ease with which deficiency syndromes appear.

Distinctive data concerning the relationship between vitamin requirement and total metabolism have been given by Cowgill² for vitamin B₁ (thiamin). His studies indicate that deficiency of this vitamin arises more readily as the total metabolism increases if the intake of vitamin B₁

remains constant. Protection against vitamin B₁ deficiency fails if there is a low vitamin B₁-calorie ratio or, as Williams and Spies¹ have suggested, a low vitamin B₁-non-fat calorie ratio. This state of affairs is common in chronic alcoholism. In this condition other factors act to enhance vitamin B₁ deficiency in the body proper but the low vitamin-calorie or non-fat calorie ratio is important in the production of polyneuritis, disorder of the heart, and other manifestations of a deficiency of this nutritional essential.

The influence of excessive calorie intake from food itself on the production of vitamin B₁ deficiency is illustrated perhaps by the following case.

The patient was a man, usually weighing 160 pounds, who had gained about 55 pounds in a year because of eating excessively, particularly of sugar and fat. He did this because he suddenly became rich and declared he had always wanted to eat "luxuriously." Signs attributable to vitamin B (complex) deficiency developed, neuritis in particular. This patient reduced his diet by omitting sugar, chocolate, butter (except about 20 grams) and olive oil, but made no other change so that the vitamin B₁ content remained about the same. His weight fell slightly more rapidly than it was gained, reaching 165 pounds 10 months later. Within two months after commencing this reduced diet, signs of neuritis and vitamin B (complex) deficiency had vanished. When the patient found that he could reduce his weight, he decided that since he enjoyed the foods omitted he would again eat excessively. His weight soon increased and polyneuritis returned, to vanish soon after he ate in a reasonable manner and partook of a concentrate of vitamin B.

THE INFLUENCE OF THE GASTROINTESTINAL TRACT

Defective diets are, of course, a most important cause for nutritional deficiency. Defective nutrition, however, can arise even when the diet seems adequate, because of some disturbance in the state of the gastrointestinal tract and its contents which may act adversely so as to "condition" or enhance a deficiency of nutritional factors within the body proper. The difficulty may depend on the improper reduction of raw materials to the correct size and constitution for absorption, as can arise for example from lack of teeth, diarrhea, or defective gastric secretion. Simple tests to determine defective absorption are needed. Failure of this normal function of the alimentary tract alone may prevent the body itself from receiving proper amounts of nutritional essentials. Furthermore, as McCarrison originally showed, widespread changes in the gastrointestinal tract can be produced by defective nutrition. Such alterations can impair absorption leading to a further deficiency of nutritional essentials and a vicious cycle is thus established. There are innumerable factors that have to do with absorption and the disturbances may be anatomical or chemical and physiological. Alterations in motor and secretory functions, the composition of the intestinal contents and the influence of effects arising from an origin external to the alimentary tract may affect absorption. One must distinguish between the effects being primary or contributory, for disease itself can cause all sorts of dysfunction of the intestinal tract. The statements

to follow simply indicate some of the known relationships between gastrointestinal function and nutrition

There is little direct evidence regarding faulty absorption from the human gastrointestinal tract but, as is indicated below, there is a considerable amount of indirect evidence. Perhaps the most direct evidence has been given by Groen's⁴ studies. He has shown, by means of intubation of the small intestine, that when glucose is kept in contact with a segment of the intestine in pernicious anemia the ability of a given area of the intestine to absorb it is definitely diminished. With improvement in the patient upon administration of liver extract this function apparently often returns to normal. Difficulty in the absorption of sugars can not be ascribed only to lack of the factor needed for manufacture of normal blood because Groen has shown a similar state of affairs occurred in cases of vitamin B₁ deficiency without anemia and diminished as the patients improved upon being given proper therapy. In a case of scurvy Groen found this function normal. It is possible that this defect is due to the lack of some component or metabolic derivative of the vitamin B complex certainly contained in crude liver extracts. Likewise Barker and Rhoads⁵ have shown that in sprue with intestinal symptoms the levels of the fat in the blood after a meal rich in fat are low, but that after the injection of liver extract the post-absorptive levels of fat in the blood approach normal.

Various organic abnormalities of the gastrointestinal tract are associated with the production of nutritional deficiency syndromes. Sometimes this results in producing chemical and physiological alterations which may be the more immediate cause for producing a deficient state or causing faulty absorption. Intestinal anastomoses and partial intestinal stenosis have been shown to be responsible for numerous different syndromes due to deficiency of vitamins and other nutritional essentials. The opportunity of correcting the organic defect by surgery has on several occasions resulted in cessation of the difficulty the body has had in obtaining or utilizing the factors it lacked. In pernicious anemia, for example, Richardson⁶ and I have observed patients with an intestinal short circuit who maintained their blood with difficulty on liver extract administered orally, but who did so relatively easily when it was given intramuscularly. These individuals were able to maintain their blood without liver extract after the intestines had been returned to essentially their normal state by operative procedures. In such instances the influence of a toxic factor arising as a result of the intestinal disturbance and acting as an inhibitory agent may be perhaps more significant than the abnormal anatomical relations handicapping absorption. In pernicious anemia usually a disturbance of a certain portion of the intestinal tract, namely the stomach, is responsible for the profound effect upon the nutrition of the individual. This is known because Castle⁷ has shown that a factor in the normal diet becomes effective in the body as "liver extract" only after interaction with a substance secreted by the normal stomach. The gastric factor is lacking in most cases of Addisonian

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pernicious anemia but a deficiency of the food factor or disorder of absorption may lead to a similar syndrome and such disorders may be contributory in classical cases of Addisonian pernicious anemia

Nutritional deficiency can disturb not only chemical and physiological functions but also cause anatomical changes in the gastrointestinal tract making it still more difficult for the body to receive the material it lacks. The lack of material found in the broader fractions of liver extract effective in pernicious anemia can lead to degenerative alterations in the gastrointestinal tract, causing atrophic changes in the tongue, esophagus, gastric mucosa, and intestines which appear clinically as signs of pernicious anemia, sprue, pellagra, and in less well defined conditions. Entirely similar alterations have been produced by Miller and Rhoads⁸ in swine on diets deficient in vitamin B₂ or a closely related substance. The lack of nutritional essentials other than those of the vitamin B complex or related substances, such as vitamins A and C, can also induce degenerative changes in the gastrointestinal tract. These anatomical changes are in large part reversed following the administration of suitable amounts of the deficient substance.

With protein deficiency, edema of the intestinal mucosa may occur, leading to difficulty in absorbing the needed protein. Diarrhea may result from edema, further handicapping absorption. The vicious cycle may also be enhanced by the intake of water and salt for they will favor the development of edema when plasma proteins are deficient. If moderately large amounts of water and salt are given by clysis when protein deficiency is present, as may be done post-operatively or following loss of much blood, edema may be precipitated or increased. Experimental work and cases illustrating these problems concerning protein deficiency have been presented clearly by C. M. Jones⁹. In this connection Strauss'¹⁰ observations on the rôle of the plasma proteins in "toxemia" of pregnancy and the value in treatment of reducing the sodium intake should be noted.

Some of the physiological and chemical alterations of the gastrointestinal tract which enhance nutritional deficiency and which may be caused by nutritional deficiency may be referred to the motor and secretory functions and to the composition of the intestinal contents. Whatever causes rapid gastric or small intestinal evacuation and alteration in the tone of these organs may diminish the amount of some nutritional factor taken into the body proper. It has been shown^{11, 12, 13} by roentgen-ray studies, that in sprue changes in tone and activity of the intestine vary with the severity of the disease, and that when liver extract is given these changes decrease and become absent as the patient improves and signs of faulty absorption decrease. These alterations are not specific and consist of distortion of the mucosal pattern and a variation in the caliber of the intestinal loops. Somewhat similar alterations and lack of haustral formation have been recorded in other conditions where dietary deficiency was considered to exist, and improvement has followed administration of vitamin B₁ and other nutritional essentials.

Inadequate secretions can prevent the body from receiving from the diet suitable amounts of some nutritional factors. The lack of bile may perhaps hinder the absorption of vitamin A and material such as vitamin K, which may be of value in forming prothrombin. The results on nutrition of a lack of Castle's gastric intrinsic factor have been mentioned. The rôle that achlorhydria plays in favoring the development or increase of nutritional deficiency is not well understood, but it undoubtedly is a factor of importance and has been suggested as playing a rôle in causing deficiency of various vitamins and some minerals, such as iron and calcium. This condition may be induced by faulty diets, for example, those rich in farinaceous food and sparing in animal protein. It has been suggested¹⁴ that lack of some factor in the vitamin B complex can induce this condition. It is common, however, in various types of vitamin and other deficient states. Hypoacidity may play a part directly or indicate a significant disturbance of absorptive capacity of the alimentary tract. Lack of hydrochloric acid may decrease the ease with which substances, for example iron, are liberated from complexes which contain them in food and alter the reaction of the intestinal contents in such a way as to handicap the absorption or utilization of substances.

The mixture inside the gastrointestinal tract can influence what the body receives. For example, large amounts of some substances such as fatty acids and phosphorus may bind other substances such as calcium and iron into insoluble forms. During digestion the combined effects of low oxygen tension, an abundance of readily oxidizable substances and an acid reaction provide conditions in which the conversion of ferric to ferrous iron (the form in which iron is absorbed) is likely to occur. The mixture of the intestinal contents may be such as to injure a nutritional factor such as vitamin C, as has been suggested by various reports^{15, 16, 17}. Like other conditions it may not be possible to alleviate scurvy by the oral administration of the needed substance but only by its injection and, in scurvy, although a disorder of absorption may occur, in rare cases a destruction of the vitamin may perhaps take place in the intestinal tract. It is possible that occasionally the intestine may contain particular substances that inhibit absorption. There are suggestions in the literature that iodoacetic acid can inhibit this function.

Effects produced on intestinal tract function from an influence arising external to this system must also be considered. Liver disease can increase the tension in the portal system and thus may affect the absorption of material derived from food. Infections may cause low absorption. Heymann's¹⁸ studies disclosed that 70 per cent of ingested carotene was absorbed by normal infants whereas only 36 per cent was absorbed in infants with infections. Sometimes the amount of a given substance in the body may perhaps determine the amount absorbed. McCance and Widdowson¹⁹ have suggested that iron metabolism is regulated by controlled absorption. They consider that the amount absorbed depends perhaps not upon the con-

centration of free ions in the lumen of the gut but upon their relative concentration in relation to the level of the plasma iron and the amount of iron in epithelial cells. The absorption of calcium can be related to vitamin D, it being impaired with vitamin D deficiency. Verzar²⁰ has presented interesting studies concerning the rôle of secretion from the adrenal cortex on intestinal absorption and suggests that celiac disease (Gee-Heiter's disease) and "non-tropical" sprue may be possibly "adrenocortical or intestinal disturbances of absorption." Studies have shown that in adrenalectomized animals a series of syntheses important for absorption and other metabolic activities are lacking, including the syntheses of fat and the transformation of lactoflavin in the intestinal mucosa to flavin phosphoric acid (one of the entities of vitamin B₂).

It is possible that some hormone of the pituitary may in part control tone and motility of the gastrointestinal tract, and the cases of pituitary disease and macrocytic anemia reported by Snapper et al²¹ have suggested to these authors that the secretion of Castle's gastric factor might be affected by some pituitary secretion. Of course many external influences can affect digestion such as exercise, emotional reactions, and the like, and such conditions always have to be reckoned with in considering function of the intestinal tract in relation to nutrition, and are particularly important to consider in the treatment of the patient himself.

THE INFLUENCE OF DEFECTIVE INTERMEDIARY METABOLISM AND INHIBITORY FACTORS

Even if the body proper has received the usual requirement of nutritional essentials, a deficiency may arise, or more often be enhanced, because of a disorder of their metabolism. The fact that some cases of pernicious anemia require much larger doses of liver extract parenterally than other cases to maintain their blood suggests differences in the intermediary metabolism of "liver extract." Cases showing intrinsic resistance to vitamin D²² and to other substances also occur when there is no entirely satisfactory explanation for the difficulty. It is well recognized that infection and severe damage to important organs can precipitate deficiency syndromes and that under such circumstances more of the materials lacking in the body must be given for cure. This applies to material given orally or parenterally so that faulty absorption is not the only way such disorders may act to handicap the action of nutritional materials. The increased metabolism resulting from fever does not seem to wholly explain the inhibitory or precipitating effect of infection. Many studies in recent years regarding the metabolism of vitamin C are among those that illustrate very well that infection decreases the amount of a nutritional essential available in the body for utilization. Here again a vicious cycle may arise for resistance to infection is lowered by poor nutrition and infection intensifies nutritional deficiency. There is some evidence that chronic fatigue also acts to hinder the utilization of nutritional material.

It is not surprising in view of the rôle played by infection in deficiency syndromes that Eijkman originally thought that vitamin B₁ deficiency was due to intoxication. The fact that large amounts of carbohydrate can impair the protective power of vitamin B₁ in relation to the nerves certainly might suggest that a toxic action was responsible for the condition. The pyruvate and lactate that accumulate from deficiency of vitamin B₁ can act as toxic substances, but they are not primarily responsible for symptoms of vitamin B₁ deficiency.²³ Failure of function of the cell from interference with its metabolism due directly to B₁ deficiency is the fundamental cause of symptoms. The rôle that two or more factors may play in causing disease is significant and toxic substances can precipitate symptoms of deficiency. Rhoads'²⁴ studies showing that indol in an amount that causes no anemia in dogs fed a normal diet can produce anemia when dogs are fed a diet which causes black tongue are most significant. The condition can be prevented and cured by liver extract. Miller and Rhoads²⁵ have also shown that the susceptibility of the canine hematopoietic function to damage by amidopyrine is influenced by diet. Substances may act perhaps to deplete reserve supplies, as has been shown experimentally by White²⁶ to be the action of iodoacetic acid on the sulphur containing amino acid reserves.

Disease of the liver can adversely affect nutrition. It can prevent the adequate storage of vitamin A and adversely affect the metabolism of carotene. The liver influences in some unknown way the metabolism of vitamin D. With severe damage to the liver it is necessary to give much larger doses of this vitamin than usual to cure rickets.²⁷ Plasma protein depletion is enhanced by liver disease. Nutritional factors can also alter liver function. The amount of fat stored in the liver can be related to the vitamin B₁ intake.²⁸ The effect of a superabundance of nutritional essentials in favorably influencing liver disease is worthy of much more study. Patek²⁹ and Goodhart and Jolliffe³⁰ among others have indicated the advantages of such treatment.

Inside the body the balance between one substance and another may influence the availability of a nutritional factor as has been noted concerning vitamin B₁ and an excess of carbohydrate. Another example is that lactoflavin has a sparing effect on vitamin B₁.³¹ If one keeps in mind the rôle that such substances as vitamin B₁ play in intermediary carbohydrate metabolism and vitamin C in the balanced chemistry of oxidation reduction, it is not difficult to visualize the many ways that may bring about the improper utilization of nutritional essentials inside the body.

DEPLETION OF NUTRITIONAL ESSENTIALS BY LOSS FROM THE BODY

It has been noted that nutritional deficiency disease arises because of a failure of consumption or utilization of essential factors. Increased chemical activity may enhance their depletion. Depletion may arise because of a defective diet, abnormality of gastrointestinal function, and disorder of inter-

mediary metabolism Damage to organs and their altered function, infections, and toxic substances may act in an inhibitory way to intensify a deficiency There is another method by which depletion of nutritional factors may arise, namely, loss from the body of the formed essentials In pregnancy some nutritional elements must be given to the fetus, thus diminishing the mother's supply Protein may be lost through the kidneys, into effusions in the peritoneal and pleural cavities and from suppuration and serous drainage from surgical wounds With loss of blood essential elements leave the body Iron deficiency is more often attributable to chronic loss of blood than to any other mechanism More than one of the different mechanisms that induce nutritional deficiency are usually active in any one case The physician should recall this in practice and attempt to correct all possible faults that might handicap nutrition

REMARKS CONCERNING DIAGNOSIS, TREATMENT, AND PARTICULARLY PREVENTION

An appreciation of the nature of nutrition and of the mechanisms involved in producing nutritional deficiency forms the background upon which diagnosis, treatment, and prevention depend There follow a few remarks concerning these aspects with especial emphasis on that most important problem, namely prevention

Nutritional failure in practice is seldom complete or simple It is often complicated by a variety of mechanisms inducing its origin or aggravating the initial abnormality The occurrence of a mild state of suboptimal nutrition or a borderline state of partial deficiency is very common and examples of classic scurvy, beriberi and the like are relatively rare Whenever there is evidence that one nutritional essential is lacking, leading to a clear cut syndrome, it is usually possible to show that deficiency of other factors exists so that multiple deficiency is the rule Signs indicative of outstanding deficiencies of two or more factors in one individual are not rare An era appears to be approaching when by quantitative chemical tests, some of which are well developed and others under study, it may be possible to appraise the nutritional status of an individual For some time yet we must be satisfied to diagnose in many instances of partial deficiency that such a condition merely exists without being able to name with any precision exactly what factors are lacking Even when outstanding signs of deficiency are present it is often impossible to state exactly what missing factor is responsible for each and every manifestation although, of course, there are certain signs characteristic of deficiency of each vitamin and mineral, and the like Multiple manifestations can be related to a single deficiency We must, however, attempt to define and learn in exactly what way symptoms and signs found in deficiency states are produced

The prevention of nutritional instability is of prime importance Often the results of pronounced deficiency are not reversible as, for example, the

bone deformities resulting from rickets, the loss of the teeth from scurvy and central nervous system degeneration in pernicious anemia. On the contrary certain defects can be repaired, such as the damaged capillaries in scurvy and the blood in pernicious anemia. It is the vague borderline states of nutritional failure of mild degree that are of great importance to recognize and correct, and here we usually have to be guided by general symptoms, a detailed history, and hints obtained from various sources including newer chemical and other tests.

The early general symptoms of nutritional deficiency are vague, a sense of fatigue or lack of energy, inefficiency, and mental irritability are common. Mild anemia and simple disorders of the digestive tract are the rule. Symptoms and signs of deficiency may be referable to essentially any tissue of the body but disorders referable to the bones, faulty growth, the gastrointestinal, neural, blood-forming and reproductive systems, and the skin are particularly common. The history may indicate that the patient is nervous, has a poor appetite, mild digestive symptoms, and is fussy and finicky regarding his choice of food. He may be in such haste that he has not time for a proper luncheon and is too tired to eat a proper meal in the evening. As a result the individual is easily exhausted and nervously unstable. The exact deficiency present can not be stated but proper food will go a long way to improve such a patient.

There is a wide range between the minimal and optimal requirement of dietary factors and studies concerning this subject are few. Those made on the utilization and retention of vitamin B₁ in children by Knott³² are significant in this respect. She has shown that a definite trend toward higher retention of vitamin B₁ accompanies higher levels of intake. The level of vitamin producing the highest retention may be considered optimal and the wide range observed between minimal and optimal requirement aids to explain the existence of mild vitamin B₁ deficiency in children and the beneficial results obtained by the addition of vitamin B₁ to the diet.

We should be alert to detect physiologic changes due to deficiency long before gross pathologic alterations appear. Such conditions as a low content of vitamin C in the blood and urine and slight subnormal ability to adapt vision to darkness (associated with insufficient amounts of vitamin A) often occur in individuals who consider themselves well and who show no other signs or symptoms associated with deficiency. These changes can be corrected by supplying the deficient substance. Although no one positively knows what harm slight physiologic alterations of nutritional factors cause in apparently otherwise normal persons, they certainly can not be looked upon as desirable conditions for health. The subtle effects produced by long standing slight nutritional defects need evaluation, but in practice they should be prevented if possible. In considering the far-reaching influences of faulty nutrition it should be recalled that there is evidence that it may affect adversely the span of life and that the undesirable effect of a faulty diet in the zone of partial deficiency may become detectable.

only after years or generations, and that a deficient diet may impair the vigor and resistance of an individual for some period after he partakes of an adequate diet. In this connection the observations of Bloomfield and French³³ on rats are of interest. They observed that comparable rats on the same defective diet showed great individual variation in weight loss. A long time after the weight loss had been restored by a normal diet the rats were subjected to the same deficient diet and the same animals which lost the most weight were the ones to do so again and even more rapidly a second time.

The activities of the League of Nations and the national alertness to the importance of proper nutrition in the development of the child, in the prevention of disease and for buoyant rather than merely satisfactory health is of great significance to mankind. Educational efforts can lead to improvement of the nutritional status of a large number of individuals, and in so doing, as McLester³⁴ has noted, the essential nature of any one food factor or group of factors must not be emphasized. Faddism is a cause of nutritional failure. The doctor must keep in mind that an optimal diet leads to better health than many usual diets with minimal requirements of some essential substances. He must not only be able to advise groups of individuals, such as pupils in school, regarding diet, but be alert to prevent nutritional disorders in a given patient. His attention, for example, to the iron, protein, and sodium intake in pregnancy will minimize anemia and toxemia. It is well to remember that since the nutritional states of mothers affect the well being of infants, the health of the whole population depends to a greater or less extent on maternal nutrition. Likewise, let us recall that at no period of life is optimal nutrition more important than in infancy and childhood, because nutritional defects so readily produced then may be at the root of disorders arising at any time later in life. The physician will observe many patients of all ages with mild symptoms where meticulous attention to diet will improve their well being. He should be conscious that a nutritional defect may exist and play a rôle of importance in many patients whom he sees when the symptoms presenting would not readily suggest that a better diet would be of distinctive value. The frequency of abortion has been shown to be diminished in individuals placed on optimal diets, and decrease of nervousness and better attention to school studies may occur when the pupil partakes of a diet unusually rich in protective foods. Faulty nutrition may act to spring a trap which aids to produce a condition which diet does not correct. Hertz and Means'³⁵ observation that pronounced weight loss may be a precipitating factor in thyrotoxicosis is of this sort. It is possible, I believe, that such a disturbance may play a rôle in an occasional case of leukemia.

If a deficiency syndrome is clear cut, specific treatment must be employed. The oral route often suffices. Today, however, the availability of preparations of vitamins for injection permits large amounts to be placed easily in the body proper and is of great value in the treatment of

severe cases and sick individuals. Satisfactory results will often be obtained only when distinctly large amounts are given. The rapid and dramatic improvement seen upon injection of vitamin B₁ in cases of heart disorder and polyneuritis associated with its deficiency and the striking effects of nicotinic acid in pellagra are among other examples of the value of modern therapy in deficiency disease. When specific therapy is given an attitude must not be taken that it is not necessary to watch the patient closely and that no more need be done than administer the substance in question. In the early days of specific treatment adverse symptoms occasionally appear arising from the material given, for example, tetany in rickets requiring the intravenous administration of calcium, and edema in pernicious anemia, about the time the patient begins to sit up, which clears as liver extract is continued. The deficient state must be met in toto and, as the patient improves following specific therapy, attention must be given to all aspects of his case.

In spite of the fact that diagnosis of the exact deficient state must be made as accurately as possible, it is often of more practical importance to recognize that the patient has nutritional deficiency than to be able to name exactly what nutritional deficiencies he has. In many cases of mild deficiency the precise condition can not be defined and in an effort to correct the condition the administration of supplements of manufactured concentrates alone will not at present solve the problem. As has frequently been stated experience tells us that a mixed diet of natural food stuffs, one especially rich in milk, green vegetables, fruit, butter, eggs and food with ample protein of good biologic value gives the best results.

CONCLUDING REMARKS

Ideally we should have no cases of nutritional deficiency to treat for if we lived in a Utopian world preventive measures would banish their existence. This would not be brought about by diet alone because, as has been discussed, there are many other factors than diet that play an important rôle in establishing nutritional deficiency in man. If, however, the optimal, *not the usual*, diet for man at all ages and under varying circumstances of his activity and environment were known, and if throughout generations each person took an ideal diet—one nicely adjusted to all its constituents at an optimal level for the best possible achievement—not only would much illness be prevented but the physical and mental development of man would be improved.

REFERENCES

- 1 McCARRISON, R. Nutrition in health and disease, Brit Med Jr, 1936, 11, 611-615
- 2 GOWGILL, G. R. The vitamin requirement of man, Yale University Press, 1934
- 3 WILLIAMS, R. R., and SPIES, T. D. Vitamin B₁ and its use in medicine, 1938, The Macmillan Co., N. Y.

- 4 GROEN, J The absorption of glucose from the small intestine in deficiency disease, *N E Jr Med*, 1938, ccxviii, 247-253
- 5 BARKER, W H, and RHOADS, C P The effect of liver extract on the absorption of fat in sprue, *Am Jr Med Sci*, 1937, cxiv, 804-810
- 6 RICHARDSON, W Pernicious anemia due to enteroenterostomy, *N E Jr Med*, 1938, ccxviii, 374-376
- 7 CASTLE, W B, and MINOT, G R Pathological physiology and clinical description of the anemias, 1936, Oxford Univ Press, N Y (See numerous references there)
- 8 MILLER, D K, and RHOADS, C P The experimental production of loss of hematopoietic elements of the gastric secretion and of the liver in swine with achlorhydria and anemia, *Jr Clin Invest*, 1935, iv, 153-172
- 9 JONES, C M Protein deficiency, *N E Jr Med*, 1936, ccxv, 1152-1155
- 10 STRAUSS, M B Observations on the etiology of the toxemias of pregnancy II Production of acute exacerbation of toxemia by sodium salts in pregnant women with hypoproteinemia, *Am Jr Med Sci*, 1937, cxiv, 772-783
- 11 MACKIE, T T, and POUND, R E Changes in the gastrointestinal tract in deficiency states with special reference to the small intestine a roentgenologic and clinical study of 40 cases, *Jr Am Med Assoc*, 1935, civ, 613-618
- 12 MACKIE, T T, MILLER, D K, and RHOADS, C P Sprue roentgenologic changes in the small intestine, *Am Jr Trop Med*, 1935, v, 571-589
- 13 MILLER, D K, and BARKER, W H Clinical course and treatment of sprue, *Arch Int Med*, 1937, lv, 385-414
- 14 JOFFE, P M, and JOLLIFFE, N The gastric acidity in alcohol addicts, with observations on the relation of the B vitamins to achlorhydria, *Am Jr Med Sci*, 1937, cxviii, 501-509
- 15 STEPP, W Vitaminmangel als Ursache und Folge von Magendarmerkrankungen, *Munchen med Wchnschr*, 1936, lxxviii, 1119-1123
- 16 EINHAUSER, M C-Vitamin und Gastroenteritis, *Ztschr f d ges exper Med*, 1936, lxxviii, 461-477
- 17 HAGMANN, E A Active scurvy in an infant receiving orange juice, *Jr Pediat*, 1937, xi, 480-483
- 18 HEYMANN, W Absorption of carotene, *Am Jr Dis Child*, 1936, li, 273-283
- 19 McCANCE, R A, and WIDDOWSON, E M Absorption and excretion of iron, *Lancet*, 1937, ii, 680-684
- 20 VERZAR, F Adrenal cortex and intestinal absorption, *Am Jr Digest Dis and Nutr*, 1937, iv, 545-546
- 21 SNAPPER, I, GROEN, J, HUNTER, D, and WITTS, L J Achlorhydria, anemia and subacute combined degeneration in pituitary and gonadal insufficiency, *Quart Jr Med*, 1937, xxx, 195-209
- 22 ALBRIGHT, F, BUTLER, A M, and BLOOMBERG, E Rickets resistant to vitamin D therapy, *Am Jr Dis Child*, 1937, liv, 529-547
- 23 MEKLEJOHN, A P, PASSMORE, R, and PETERS, R A Pyruvic acid and vitamin B₁ deficiency, *Biochem Jr*, 1932, xxvi, 1872-1879
- 24 RHOADS, C P Effect of indol on hematopoiesis in dogs fed deficient diets, *Proc Soc Exper Biol and Med*, 1937, xxxvi, 652-654
- 25 MILLER, D K, and RHOADS, C P The effect of diet on the susceptibility of the canine hematopoietic function to damage by amidopyrine, *Jr Exper Med*, 1937, lxxvi, 367-382
- 26 WHITE, A Iodoacetic acid and sulfur metabolism, *Science*, 1937, lxxvi, 588
- 27 HEYMANN, W Importance of the liver for the antirachitic efficacy of vitamin D, *Proc Soc Exper Biol and Med*, 1937, xxxvi, 812-814
- 28 MCHENRY, E W Vitamin B₁ and the synthesis of fat from carbohydrate, *Science*, 1937, lxxvi, 200 *Ibid* Vitamin B₁ and fatty livers, *Jr Physiol*, 1937, lxxix, 287-295
- 29 PATEK, A J Treatment of alcohol cirrhosis of the liver with high vitamin therapy, *Proc Soc Exper Biol and Med*, 1937, xxxvii, 329-330

- 30 GOODHART, R, and JOLLIFFE, N J Effects of vitamin B (B₁) therapy on the polyneuritis of alcohol addicts, Jr Am Med Assoc, 1938, cx, 414-418
- 31 ELLIS, L N, and ZMACHINSKY, A The sparing action of lactoflavin on vitamin B₁, Science, 1937, lxxvi, 245-246
- 32 KNOTT, E M A quantitative study of the utilization and retention of vitamin B by young children, Jr Nutr, 1936, xii, 597-611
- 33 BLOOMFIELD, A L Individual variations in susceptibility to dietary deficiency, Jr Nutr, 1937, xiv, 111-116
FRENCH, L R, and BLOOMFIELD, A I "Latent deficiency" in rats Variations in weight loss on repeated feeding of a defective diet, Jr Nutr, 1937, xiv, 117-129
- 34 MCLESTER, J S Nutrition problems in education, Jr Am Med Assoc, 1937, cix, 838-839
- 35 HERTZ, S, and MEANS, J H Pronounced weight loss as a precipitating factor in thyrotoxicosis, West Jr Surg, 1936, xlv, 534-537

STUDIES ON THE PATHOLOGICAL PHYSIOLOGY OF THE EXOPHTHALMOS OF GRAVES' DISEASE¹

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THE chronic progressive exophthalmos of the type seen in Graves' disease, even when uncomplicated, is obviously a highly complex phenomenon, perhaps as complex etiologically as Graves' disease. Although both have been studied for more than a century they are still involved in doubt and controversy.

My primary interest in the study of exophthalmos has been the hope that a further understanding of this symptom might throw additional light on the etiology of Graves' disease. There is also the immediately practical question of how to continue subtotal thyroidectomy in the treatment of Graves' disease and at the same time prevent the occasional development of so-called "paradoxical" or "malignant" exophthalmos.

The exophthalmos of Graves' disease is a chronic, progressive, bilateral protrusion of the orbital contents. One says 'bilateral,' though rarely it is unilateral, and usually it is not symmetrical, either in man or in animals—of the animals so far studied it is most asymmetrical in the guinea pig. This form of exophthalmos is also seen occasionally in human rickets¹ and may be produced experimentally in the severe low P rickets in rats (Thompson²). It is also seen in acromegaly,³ in the leukemias,⁴ in chronic nephritis,⁵ and in experimental chronic renal insufficiency. Possibly, the forms seen in congenital syphilis⁶ and in the Hand-Schaller-Christian syndrome⁷ may be of this type. Exophthalmos is usually a late symptom in all of these diseases, just as in Graves' disease. It is present in about two-thirds of the cases of primary Graves' disease, i e , below the age of 45, but it is relatively infrequent in those cases developing during the decline of sexual life (toxic adenoma, adenomatous goiter, iodine Basedow, menopausal Graves'), so that if all cases, irrespective of age and sex are included, it is present in about one-third of the cases.

ETIOLOGY

Basedow⁸ thought it was due to a hypertrophy of the cellular tissues in the orbit. Sattler,⁹ W Krauss¹⁰ and many others thought it was due to venous congestion and edema. After the demonstration by Askanazy¹¹ of fatty degeneration of the recti muscles in Graves' disease and the occurrence of a chronic inflammatory swelling of these muscles in the late stages of severe exophthalmos (Naffziger¹²), the view that the exophthalmos was due to enlargement and weakness of these muscles was advanced. Supplementing all these theories is the idea that an increased normal or

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abnormal thyroid secretion is also necessary. None of these theories is now considered of primary importance, since the exophthalmos, at least in its earlier stages, shows considerable variation from day to day, both in man and animals, and also may disappear after death, or under general anesthesia, or after section of the cervical sympathetic. However, the degenerative and inflammatory changes mentioned above are unquestionably important secondary, complicating, and even contributing factors, but in my opinion are always the result and never the cause of exophthalmos.

The experimental study of exophthalmos began in 1858 with the discovery of H. Muller¹³ of the smooth muscles of the orbit of mammals. Muller recognized two groups of these muscles: (1) *peri-orbital*, and (2) *palpebral muscles*. The *peri-orbital muscle* is well developed in lower mammals and consists of a muscular cone whose base is attached to the orbital septum and bony rim of the orbit and whose apex is attached to the ring of Zinn. In amphibians, reptiles, birds and some aquatic mammals (seal, dolphin) the muscle fibers have cross striations. This is a powerful muscle and envelops the entire contents of the orbit except the lacrimal gland. In the lower mammals it is capable of pushing the orbital contents forward when electrically stimulated in spite of the normal antagonism of the recti and retractor bulbi muscles. This was first demonstrated by Wagner in 1859¹⁴ and more extensively studied by Claude Bernard, Aran and others. MacCallum and Cornell¹⁵ (1904) by removing the roof of the orbit in the dog and stimulating the cervical sympathetic, observed typical smooth muscle contraction waves passing back over the muscle.

In man and the anthropoids, the *peri-orbital muscle* is vestigial and because of this most students have rejected the idea that its contraction can have any influence on the position of the orbital contents in man. We know that cutting the cervical sympathetic causes a Horner's syndrome in man just as in animals, although the ensuing enophthalmos is not quite so striking in man. The *palpebral muscles* of Muller are present in both the upper and lower lids only in man and anthropoids. In the lower mammals palpebral muscles composed of smooth muscle fibers occur only in the lower lid and in some mammals (seal and dolphin) these muscles also are striated. These involuntary palpebral muscles in man form an incomplete ring around the globe (Hesser¹⁶) and ancestrally are derived from the striated recti muscles. In 1907 Landstrom¹⁷ described a cylinder of smooth muscle fibers inserted into the fascia of the globe near its equator and extending anteriorly to the orbital septum. Evidence for separating such a group of muscle fibers from the palpebral muscles of Muller seems inadequate. No one doubts that lid-lag (von Graefe's sign) and widening of the palpebral fissure (Stellwag's and Dalrymple's signs) are principally due to increased tone of the palpebral muscles of Muller. It is only the protrusion of the globe in man by the increased tone of the vestigial *peri-orbital muscle* that is doubted, even though section of the cervical sympathetic may instantly abolish the exophthalmos and lid spasm and produce

exophthalmos in man as well as in animals. As above mentioned, this muscle is fully capable of protruding the orbital contents in the lower mammals, but in man and in monkeys it seems to be inadequate and one has to invoke the additional factor of a weakness of the recti or antagonistic muscles to account for the exophthalmos of Graves' disease.

The sympathetic innervation of the muscles of Muller as shown by Claude Bernard may be represented schematically by ganglion cells in the lateral horns of the spinal cord, whose axones emerge at the level of the first and second dorsal vertebrae, and end around the ganglion cells of the superior cervical ganglion from which the postganglionic fibers extend to the muscles. In 1909 Karplus and Kreidl¹⁸ showed that stimulation of the hypothalamus in cats, laterally and slightly posterior to the infundibulum, caused maximum dilatation of the pupil, widening of the palpebral fissure, and thus established true sympathetic representation in the hypothalamus. The pathway from the hypothalamus to the lateral horns of the spinal cord is unknown.

In 1910 Gley^{18a} reported the development of exophthalmos in one male puberal rabbit following thyroidectomy. In 1931 Schockaert,¹⁹ working with baby ducks, and Loeb and his co-workers,²⁰ using young guinea pigs (adults are highly resistant), observed that exophthalmos developed in from seven to ten days following the daily injection of anterior pituitary extracts. In 1932 Marine, Baumann, Spence and Cipra²¹ reported the occurrence of exophthalmos in puberal rabbits that developed parenchymatous goiter on a diet of alfalfa hay and oats and the daily intramuscular injection of 0.1 c.c. or more of methyl cyanide. The fact that exophthalmos did not develop until large parenchymatous goiters appeared and that such goiters were associated with hypertrophy of the anterior pituitary of the type seen after thyroidectomy suggested that there was a close association between thyroid deficiency and increased activity of the anterior pituitary and exophthalmos. Accordingly, we removed the thyroid from rabbits and found that exophthalmos was more easily and more quickly produced.²² By analogy it also seemed likely that the production of exophthalmos in guinea pigs by anterior pituitary extracts would be facilitated by thyroidectomy. This also was found to be true and indicates that the exophthalmos promoting effect of anterior pituitary extracts is brought about by action on other end organs than the thyroid.²³ Smelser has reported similar observations.²⁴ The observations of Friedgood²⁵ on guinea pigs further confirmed the importance of thyroid deficiency. He found that the best exophthalmos produced by anterior pituitary extracts developed after the metabolic rates had fallen below normal. It was now established that the thyroid hormone took no positive part in the production of exophthalmos and also that some substance produced in the anterior pituitary was directly, or indirectly through its interrelations, responsible for the exophthalmos, possibly by acting on a sympathetic nervous mechanism within the central nervous

system (hypothalamus) Pituitary extracts will not produce exophthalmos if the cervical sympathetic is cut

It is well known that exophthalmos cannot be produced by the administration of thyroxine or desiccated thyroid either in man or in animals, despite occasional positive reports in the literature (Notthafft,²⁶ Brain²⁷) Indeed, the opposite is true Thyroxine offers specific protection against the development of exophthalmos in rabbits, guinea pigs and probably man It has also been shown that this form of exophthalmos may be cured in



FIG 1 March 6, 1935 Moderate exophthalmos post-thyroidectomy Males

rabbits by thyroxine (figure 2), and there is considerable evidence that thyroxine is beneficial in human exophthalmos In the presence of abundant thyroid tissue, iodine is as effective as desiccated thyroid in preventing exophthalmos in rabbits and guinea pigs, and there is rapidly accumulating evidence that the present wide-spread use of iodine in the treatment of Graves' disease is gradually reducing the incidence of exophthalmos in Graves' disease Plummer and Wilder²⁸ report a drop from 69 to 40 per cent in the incidence of exophthalmos since 1922 The mechanism of exophthalmos production appears to be due to the action of an excess of some anterior pituitary hormone directly, or indirectly through the gonads, on a sympathetic center in the hypothalamus Such stimulation of the sympathetic center apparently becomes effective only when thyroxine is greatly

decreased, which suggests that such centers are held in a delicate balance by the interaction of many hormonal factors. Thyroid insufficiency, relative or absolute, therefore, is a necessary condition in order that this form of exophthalmos may develop, yet it does not occur in the severe thyroid deficiencies of endemic cretinism or in Gull's disease. It is obvious, therefore, that other factors than thyroid deficiency and hyperactivity of the anterior pituitary are involved. We have many times pointed out that sex and age are important. In rabbits it is produced most easily at the age of puberty and is approximately 20 per cent more frequent in males. We have also



FIG 2 April 23, 1935 Same rabbits as in figure 1, 48 days later, after having received 0.2 gm desiccated thyroid daily during this period

pointed out that those rabbits which develop the best exophthalmos are sexually more active. In view of the age and sex differences and of the increased sexual development following thyroidectomy in puberal rabbits, we have studied the effect of gonadectomy on the development of the exophthalmos, and found that no frank exophthalmos developed in 38 adult male and 23 adult female rabbits after gonadectomy.²⁹ We have also studied the effect of gonadectomy on the regression of exophthalmos in nine male rabbits and found that it regressed completely within three to five weeks, whereas it was unchanged in the controls. One of the rabbits in which regression occurred following gonadectomy had had exophthalmos

continuously for 45 months despite bilateral cryptorchidism and later unilateral orchidectomy. Attempts to analyze the sex gland factor have been made by means of cryptorchidism, by which we attempted to split the possible effect of the germinal epithelium from that of the interstitial cells. We found that exophthalmos did not recede in cryptorchid rabbits even after six months³⁰. The evidence so far obtained indicates that the germinal epithelium has little, if anything, to do with the development of exophthalmos, but that the degree of functional activity of the interstitial cells is an important factor in determining the development of exophthalmos. It further suggests that the absence of exophthalmos in myxedema and in cretinism may be in some way related to the lack of development of sufficient internal secretion of the gonads as in cretinism or to the loss of some of these internal secretions as in myxedema. Following up the evidence that the interstitial cells of the testis were producing some hormone which in association with reduced thyroid secretion, increased pituitary activity and perhaps other endocrine and mineral imbalances was capable of maintaining an existing exophthalmos, we have carried out experiments on rabbits using testosterone propionate, androsterone and dehydro-androsterone. Only in rabbits that had had exophthalmos and recovered or had latent exophthalmos or had mild exophthalmos did the administration of these androgens increase or produce exophthalmos. The reactions were greatest with testosterone propionate and least with dehydro-androsterone. Feeding desiccated thyroid counteracts the exophthalmos promoting effect of the androgens.* In no instance was exophthalmos produced in rabbits that had never had exophthalmos, irrespective of whether they had been subjected to thyroidectomy, thyroid feeding, cryptorchidism or gonadectomy, suggesting that other factors must be favorable in order to obtain exophthalmos with androgens. These observations suggest that the promoting effect of androgens on exophthalmos may be an important factor in the percentile increase in the incidence of post-thyroidectomy exophthalmos in Graves' disease in males.

Why female rabbits are more resistant to the development of exophthalmos is not known, although it is tempting to suggest that the protection which oestrone gives to the anterior pituitary and its antagonistic action to androgens may be factors. The fact that exophthalmos often becomes more pronounced during menstruation, at which time the blood oestrogens are at their lowest level and the androgens relatively high, may be significant. Also in this connection the increased incidence of Graves' disease during and after the menopause is suggestive. The administration of oestrone, 100 R U, twice daily for two months to male rabbits with fully developed exophthalmos, however, has not noticeably influenced it. There are, on the other hand, several reports of human exophthalmos having been benefited by oestrogenic substance (Halpern, 1933³¹).

* This finding can be correlated with the well known depressing effect of thyroxine or desiccated thyroid on the gonads (depresses ovulation and spermatogenesis in rats and produces hen feathering in male birds).

Other factors are also involved. For example, the diets necessary to produce experimental goiter and exophthalmos are abnormal, particularly as regards calcium and phosphorus ratios. Reference has already been made to the occurrence of exophthalmos in high Ca low P rickets, and since the work of Aub and coworkers³² we know that great calcium and phosphorus losses occur in typical Graves' disease, even to the occurrence of osteoporosis. Pugsley and Anderson³³ have confirmed Aub's human observations in the experimental Graves' disease-like syndrome of rats and guinea pigs produced by anterior pituitary extract. Since variations in the Ca and P ratios (particularly high P and low Ca) greatly increase the irritability of nerve and muscle cells (tetany) it is possible that the abnormal



FIG 3 July 16, 1935 Same rabbits as figures 1 and 2. Recurrence of exophthalmos after stopping desiccated thyroid

Ca and P metabolism may be a basic factor, although nothing definite is known at present.

Finally there are some practical features that should be mentioned. It has been known since partial thyroidectomy was first introduced into the therapy of Graves' disease that occasionally exophthalmos developed or increased after the thyroidectomy. The more recent subtotal thyroidectomies associated with subnormal metabolic rates have undoubtedly further increased the incidence of post-thyroidectomy (so-called malignant or paradoxical) exophthalmos. I have collected 56 reports of such cases from the literature of the last 10 years, and in the light of the sex difference and the experimental effects of androgens, castration and cryptorchidism on exoph-

thalmos of rabbits it is significant that 60 per cent of these human cases were also in males. As regards treatment, the only medical measures that have been found beneficial are iodine and desiccated thyroid in large doses. In the light of our experiments oestrogenic substance might be combined with iodine in the attempt to further depress anterior pituitary and gonadal function in these cases. In the experimental exophthalmos of rabbits iodine in the presence of sufficient thyroid tissue or desiccated thyroid in large doses

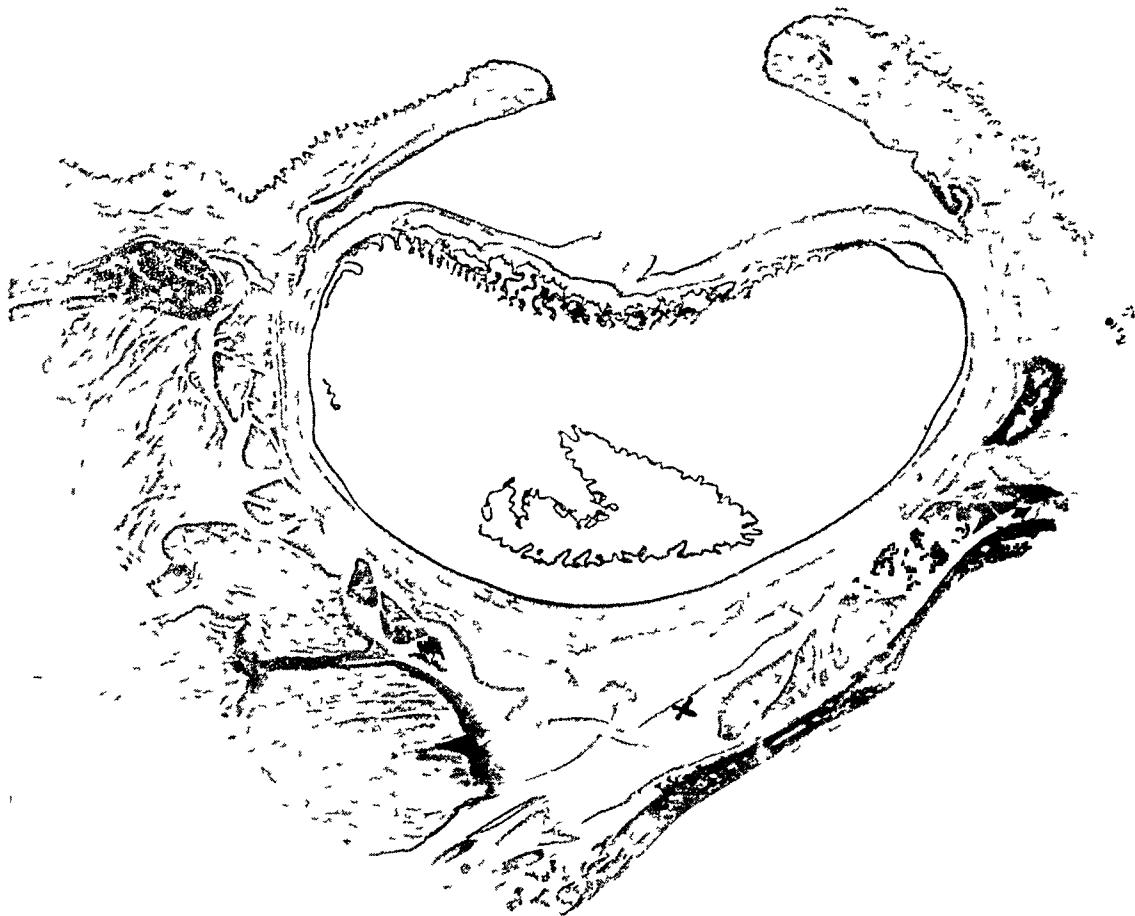


FIG 4 Sagittal section rabbit's orbit sufficiently external to the mid-line to show the *musculus orbitalis* (marked X) as a continuous band from superior to inferior orbital ridges

usually effects a cure (figures 1, 2, 3). In the human cases little success has been reported from the use of desiccated thyroid but most of these cases doubtless were complicated by secondary degenerative and inflammatory changes in the orbital tissues. On the other hand it may be readily prevented in rabbits and guinea pigs by iodine and desiccated thyroid. No thyroid insufficiency, no exophthalmos. All the recent literature reports indicate that it is being prevented in Graves' disease by the more extensive use of iodine that has taken place during the past 15 years. The mode of action of iodine

and thyroxine in preventing exophthalmos, I believe, is due to the maintenance of normal oxidation processes which in turn protect the pituitary and gonads from hyperactivity and in some unknown way this balance of pituitary-gonad-thyroid interrelations protects essential sympathetic nerve centers in the hypothalamus

Regarding surgical treatment, division of the cervical sympathetic or removal of the superior cervical ganglion has been performed by Jaboulay,⁷⁴ Jonnesco⁷⁵ and C H Mayo⁷⁶ in man. In the experimental exophthalmos of rabbits and guinea pigs this operation completely and immediately abolishes the exophthalmos but in human cases it would not be justified in the mild uncomplicated cases where it would be effective, and it would be ineffective in those complicated by extensive organic changes in the orbital tissues. In this group the drastic operations of Naffziger and others may be indicated when life saving measures are necessary.

SUMMARY

Thyroid insufficiency (relative or absolute) and anterior pituitary hyperactivity appear to be two of the essential factors underlying the development of the exophthalmos of Graves' disease. Yet the fact that exophthalmos does not occur in myxedema and cretinism clearly indicates that other factors than thyroid insufficiency and pituitary hyperactivity are necessary. Evidence has been reported indicating a definite sex difference in the incidence of thyroidectomy exophthalmos in both man and rabbits and that an increase in the functional activity of the interstitial cells and possibly of the adrenal cortex is necessary. Thyroidectomy with its ensuing increase in sex gland activity, mediated both as a direct gonad-thyroid interrelationship and as an indirect one through the pituitary, and also the parenteral administration of synthetic androgens promote the development of exophthalmos in the rabbit. Gonadectomy abolishes and cryptorchidism maintains an existing exophthalmos in the rabbit. Disturbances in Ca and P metabolism (especially high P and low Ca) affecting neuromuscular irritability appear to be necessary additional factors.

BIBLIOGRAPHY

- 1 RAINES, L. Eye symptoms in rachitis, *Arch Pediat*, 1930, *xlvii*, 55-57
- 2 THOMPSON, J. The influence of calcium and iodine on growing rats, *Endocrinology*, 1933, *xvii*, 537-549
- 3 WEIDLER, W. B. Acromegaly with extreme degree of exophthalmos, *Boston Med and Surg Jr*, 1916, *clxiv*, 506
- 4 REESE, A. B., and GUY, L. Exophthalmos in leukemia, *Am Jr Ophth*, 1933, *xvi*, 718-720
- 5 BARKER, L. F., and HANES, F. M. Exophthalmos and other eye signs in chronic nephritis, *Am Jr Med Sci*, 1909, *cxliiii*, 669-684
- 6 HALTENHOFF. Exophtalmie congenitale syphilitique, *Ann d'ocul*, *Brux*, 1889, *cii*, 108-110
- 7 BEHR, C. Über die Augenveränderungen bei der Schuller-Christian-Handschen Erkrankung, *Arch f Ophth*, 1937, *cxlvi*, 403-433

- 8 VON BASLDOW Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle, Wchnschr f d ges Heilk, 1840, vi, 197, 220
- Die Glotzaugen, Ibid, 1848, iv, 769-777
- 9 SATTLER, C Über den sogenannten Landstromschen Muskel und seine Bedeutung für den Exophthalmus bei Morbus Basedowii, Ber d ophth Gesellsch, Heidelberg, 1911, p 181
- 10 KRAUSS, W Zur Anatomie der glatten Muskeln der menschlichen Augenhöhle nach Untersuchungen am Neugeborenen I Die Membrana orbitalis muscosa, Arch f Augenh, 1912, lxi, 277-306
- 11 ASKANAZY, M Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii, insbesondere über die dabei auftretende Muskelerkrankung, Deutsch Arch f klin Med, 1898, lxi, 118-186
- 12 NAFFZIGER, H C Pathologic changes in orbit in progressive exophthalmos, with special reference to alterations in extra-ocular muscles and optic disks, Arch Ophth, 1933, xi, 1-12
- 13 MULLER, H Einige Bemerkungen über die Binnenmuskeln des Auges, Arch f Ophth, 1858, iv, 2 abth, 277-285
- 14 WAGNER, R Notiz über einige Versuche am Halstheile des sympathischen Nerven bei einer Enthaupteten, Ztschr f rat Med, 1859, v, 3 Reihe, 331-333
- 15 MACCALLUM, W G, and CORNELL, W B On the mechanism of exophthalmos, Med News, 1904, lxxv, 732-736
- 16 HESSER, C Der Bindegewebsapparat und die glatte Muskulatur der Orbita beim Menschen im normalen Zustande, Anat Hefte, Wiesb, 1913, xlix, 1-302
- 17 LANDSTROM, J Über Morbus Basedowii eine chirurgische und anatomische Studie, These, Stockholm, 1907
- 18 KARPLUS, J P, and KREIDL, A Gehirn und Sympathicus, Pfluger's Arch, 1909, cxxix, 138-144
- 18 (a) GLEY, E De l'exophtalmie consecutive a la thyroïdectomie Presentation d'animaux, Compt rend Soc de biol, 1910, lxxviii, 858-862
- 19 SCHOCKAERT, J A Hyperplasia of thyroid and exophthalmos from treatment with anterior pituitary in young duck, Proc Soc Exper Biol and Med, 1931, xxix, 306-308
- 20 LOEB, L, and FRIEDMAN, H Exophthalmos produced by injections of acid extract of anterior pituitary gland of cattle, Proc Soc Exper Biol and Med, 1932, xxx, 648-650
- 21 MARINE, D, BAUMANN, E J, SPENCE, A W, and CIPRA, A Production of goiter and exophthalmos in rabbits by administration of cyanide, Proc Soc Exper Biol and Med, 1932, xxx, 822-823
- 22 MARINE, D, ROSEN, S H, and CIPRA, A Further studies on the exophthalmos in rabbits produced by methyl cyanide, Proc Soc Exper Biol and Med, 1933, xxx, 649-651
- 23 MARINE, D, and ROSEN, S H Exophthalmos in thyroidectomized guinea pigs by thyrotropic substance of anterior pituitary, and the mechanism involved, Proc Soc. Exper Biol and Med, 1933, xxx, 901-903
- 24 SMELSER, G K Experimental production of exophthalmos resembling that found in Graves' disease, Proc Soc Exper Biol and Med, 1936, xxxv, 128-130
- 25 FRIEDGOOD, H B Experimental exophthalmos and hyperthyroidism in guinea pigs Clinical course and pathology, Bull Johns Hopkins Hosp, 1934, liv, 48-74
- 26 NOTTHAFT, A Ein Fall von artifiziellem akutem thyreogenem Morbus Basedow, zugleich ein Beitrag zur Frage der Schilddrüsenfunktion und zur Frage der Aetiologie des Morbus Basedow, Centralbl f inn Med, 1898, xiv, 353-379
- 27 BRAIN, W R Exophthalmos following administration of thyroid extract, Lancet, 1936, i, 182-186
- 28 PLUMMER, W A, and WILDER, R M Etiology of exophthalmos, constitutional factors, with particular reference to exophthalmic goiter, Arch Ophth, 1935, xiii, 833-852

- 29 MARINE, D, and ROSEN, S H Influence of gonads on exophthalmos in rabbits, Proc Soc Exper Biol and Med, 1936, *xxx*, 354-356
- 30 MARINE, D, and ROSEN, S H Effects of cryptorchidism and castration on exophthalmos in rabbits and guinea pigs, Am J Physiol, 1938, *cxxi*, 620-624
- 31 HALPERN, L Über Rückbildung von Exophthalmus durch ovarielle Behandlung Ein Beitrag zur Korrelation der Hormone von der Therapie her, Med Klin, 1933, *xxv*, 808-810
- 32 AUB, J C, BAUFER, W, HEATH, C, and ROFFS, M Studies of calcium and phosphorus metabolism III The effects of the thyroid hormone and thyroid disease, Jr Clin Invest, 1929, *xii*, 97-137
- 33 PUGSLEY, L I, and ANDERSON, E M The effect of the growth and thyreotropic hormones of the anterior pituitary upon the calcium metabolism of the rat, Am Jr Physiol, (Proceedings), 1934, *cx*, 85
- 34 JABOULAY La methode et les procedes de traitement du goitre exophthalmique par la section du sympathique cervical, Lyon med, 1897, *lxxvi*, 251-256
- 35 JONNESCO, T The enduring results of total bilateral resection of the cervical sympathetic in Basedow's disease, Internat Clin, Phila, 1903, *i*, 136-148
- 36 MAYO, C H The surgical treatment of exophthalmos, Jr Am Med Assoc, 1914, *lxiii*, 1147-1148

PHYSIOLOGICAL METHODS IN THE DIAGNOSIS AND TREATMENT OF ASTHMA AND EMPHYSEMA *

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THE purpose of this paper is (1) to describe the diagnostic value of a quantitative and qualitative study of the pulmonary ventilation when employed as a test of respiratory function, (2) to report on the results of physiologically directed therapy in asthma and pulmonary emphysema with especial reference to the evaluation of this treatment by measurements of pulmonary function. For a more general review of the subject, especially the provocative concept of intrinsic lung function, the reader is referred to the recent paper of Miller and Rappaport¹. The preliminary remarks which we venture are based on our own interpretation of the studies of other investigators and ourselves.

In an attack of asthma the diameter of the small bronchi is reduced at first as a result of spasm of the constrictor muscles. The swiftly elevated negative pressure within the chest, which has become necessary to move air inward against an obstruction, exerts a cupping action on the mucous membrane resulting in congestion and edema of the bronchial wall which further narrows the lumen of the smaller respiratory passageway. Still later, a further development of this physical influence is a sero-mucus which enhances respiratory obstruction until it is coughed up.

A more favorable consequence of the increased negative pressure within the chest during inspiration is the enlargement of the size of the bronchi during this cycle whereas during expiration the lumen of the bronchi suffer relative constriction². To this alteration in pressure during the respiratory cycle may be traced the explanation of the long-drawn out character of expiration in asthma, powerful expiratory efforts result in even greater narrowing of the bronchi and still further delay the egress of air, as will be shown later. Moreover, in severe asthma the quantity of air delivered during the act of exhalation is at times less than that moved *into* the chest, and the alveoli become increasingly distended. Over a long period of time the chest adapts itself to the increased lung volume and assumes its characteristic barrel shape, pulmonary emphysema is the end result.

This type of functional emphysema needs to be sharply distinguished from hypertrophic pulmonary emphysema in which the primary pathogenic factor is a loss of elasticity of the alveolar membrane due to degeneration or infection of the elastic tissue. Some degree of bronchial obstruction is frequently present as an added factor, due to congestion and edema of the bronchial mucous membrane or to spasm of the constrictor muscles, but the

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essential disturbance is an impaired retractility of the lung, with its inevitable train of over-distended alveoli, reduced capillary circulation, increased residual air and limitation in chest movement. As a result of large collections of air residing in portions of the lung which have a functionless alveolar membrane or a deficient blood supply, or a combination of both, an adequate exchange of oxygen and carbon dioxide is imperilled. An increased volume of air movement becomes necessary for the maintenance of this gas exchange, this calls for additional active contraction of the muscles of inspiration and expiration. The consciousness of increased respiratory effort gives rise to the sensation of dyspnea.

In an attack of asthma the sensation of dyspnea takes place immediately upon the recognition of resistance to the free passage of air and the consequent necessity for a greater effort on the part of the respiratory musculature. The heightened negative chest pressures result not only in congestion and edema in the bronchial walls, and in the alveoli as well, but in profound modifications in the circulation. Blood leaves the left ventricle in relatively smaller amounts during the inspiratory cycle, held back by the suction pressure in the lung at this time, and tachycardia and, ultimately, circulatory failure may result. Any procedure which decreases the negative pressure necessary for movement of air past the point of obstruction tends to prevent the pathological changes in the respiratory and circulatory systems. The clinical and experimental evidence for the views here expressed have been reviewed in full too recently to warrant their reproduction in this article.³

METHODS OF INVESTIGATION

A quantitative and qualitative study of the pulmonary ventilation has been employed to determine the response of the dyspneic patient to inhalation of various gases. A Benedict-Roth basal metabolism apparatus was used to record graphically the changes in pulmonary ventilation. A high speed drum was connected to the apparatus in order to reveal the qualitative alterations during inspiration and expiration. It is important to employ a motor blower unit to circulate the atmosphere to be tested since the slight resistance produced by breathing through rubber tubing introduces an error in some patients with asthma and pulmonary emphysema. The total pulmonary ventilation was measured by the device reported by Reichert⁴ in which a counter is attached to the balance wheel of the metabolism apparatus, this records each inspiration quantitatively and makes possible an immediate calculation of the total pulmonary ventilation at the conclusion of the test. A level respiratory graph and a constant oxygen concentration of the atmosphere being tested was obtained by the use of an apparatus reported by Eckman and Barach⁵ in which an automatic feed of oxygen exactly proportional to the patient's requirements is provided. The vital capacity was recorded on both the low and high speed drums in order to

measure it quantitatively and to visualize variations in inspiratory and expiratory velocity

The amount of air breathed per minute and the form of the respiratory graph were thus graphically recorded. The physiological effects of various types of inhalational therapy could be discerned by comparison with the control graphic records before treatment. The changes resulting from inhalation of helium-oxygen mixtures with and without positive pressure have been shown in previous reports⁶. In this paper the pulmonary ventilation test has been used to illustrate the physiological effects of inhalation of oxygen-enriched air atmospheres in patients with pulmonary emphysema, and the inhalation of vaporized adrenalin and neo-synephrin in patients with asthma and pulmonary emphysema.

The blood gases were measured by the method of Van Slyke and Neill⁷.

HELIUM-OXYGEN THERAPY

Helium was proposed as a therapeutic gas in obstructive dyspnea because of its decreased specific gravity in relation to nitrogen⁶. When obstruction exists in the respiratory tubal system, increased pressures become necessary for the movement of air past the point of obstruction. Since the velocity of movement of a gas through constricted orifices is proportional to the square root of the density of the gas the pressure required for the movement of an 80 per cent helium-20 per cent oxygen mixture is almost one-half that required for air. This has been experimentally confirmed in human subjects who breathe through narrow orifices and indicates that a helium-oxygen atmosphere may compensate for approximately a 50 per cent reduction in the normal diameter of the larynx or trachea. When the obstruction is continued in a linear direction throughout the smaller branches of the bronchial tree, the relief obtained by breathing a helium-oxygen mixture is less than when the obstruction is more localized. This is accounted for by the fact that the viscosity of helium is not essentially different from that of nitrogen. The clinical improvement resulting from inhalation of helium-oxygen mixtures has been described in patients with asthma and obstructive lesions in the larynx, trachea and bronchi^{6, 3b}. In a series of 105 cases of obstructive dyspnea due to lesions in the upper air passages encountered during anesthesia, Eversole⁸ reported that complete relief was obtained in 55 cases, partial relief in 37, with no relief in 13 cases. There were five additional cases in which partial respiratory paralysis occurred during spinal anesthesia. The paralysis was evidenced by absence of intercostal activity and the use of accessory muscles of respiration, the patients themselves found breathing difficult. In all of these cases breathing was said to be much easier when the helium-oxygen mixture was administered than when either air or pure oxygen was given.

The usefulness of helium-oxygen therapy is illustrated in the accompanying table (table 1) in which the clinical state of 13 patients with severe

TABLE I
The Clinical State of Patients with Severe Asthma before and after Helium-Oxygen Therapy

No	Age	Sex	Duration of Asthmatic History	Probable Etiologic Factors	Clinical State before Treatment	Method Used	Duration of Treatment	Clinical Results
1	43	M	8 months	Dust	In hospital for five weeks previous to treatment. Responded well to four days filtered air. On removal patient became worse. Filtered air then gave no relief. For a week previous to helium therapy patient became progressively worse, finally not responding to adrenalin. Patient comatose and very cyanotic.	Rebreather with mask and mouthpiece—75% helium, 20% oxygen. Intermitent treatments $\frac{1}{4}$ to 2 hours in length five to nine times daily. 2-3 cm pressure.	4 days	After five hours of treatment patient began to respond to adrenalin. Color improved. Complete response to adrenalin established in four days. Remained in hospital for eight weeks, then discharged. Readmitted two weeks later. He remained 10 weeks receiving roentgen ray therapy. Discharged improved.
2	55	M	15 years	Bacterial allergy	Two weeks previously had had left frontal sinusotomy. Severe asthma for following two weeks receiving injections of adrenalin daily with poor response. Wheezing constantly.	Rebreather with mouthpiece 75% helium, 20% oxygen. 2 cm pressure. 2-4 half-hour treatments daily.	6 days	Marked subjective and objective relief. Responded to adrenalin after two days treatment with no residual wheeze. Remained in hospital four weeks after helium treatment receiving sinus treatment. On discharge he was getting 6-10 adrenalin injections daily for residual asthma.
3	35	F	6 years	Dust	Continuous asthma unrelieved by adrenalin for two weeks.	Rebreather with mouthpiece 75% helium, 20% oxygen. 2-5 cm pressure. 3-12 half hour treatments daily.	6 days	Complete relief from dyspnea. Chest completely cleared in three days. Patient discharged two weeks later without having had any adrenalin excepting dose on admission during stay in hospital. Readmitted once again with same result. Remained in hospital for nine weeks for vaccine therapy. Received occasional dose of ephedrine 0.05 gm per day. Discharged improved. Filter in-stalled at home resulted in almost complete cessation of asthma during following year.
4	62	M	2-3 years	Pollen dust	Had continuous asthma for 18 hours when admitted to Overnight Ward. During acute attack he went into a spastic state and stopped breathing. Given 1 ml of adrenalin and artificial respiration and then began breathing two times per minute. Pulse imperceptible. Appeared to be a hopeless case. Marked acute pulmonary distention.	Helium hood. Helium 70% oxygen 25% 3 cm pressure.	18 $\frac{1}{2}$ hours	In one half hour the patient's respirations were 22 per minute, pulse was strong and regular. Six hours later patient could be aroused but he still remained in spastic state. Later patient aroused completely but was irritable at times. Twenty-four hours after start of helium treatment there was marked improvement. Forty eight hours later completely free from asthma and he received no adrenalin during the subsequent two weeks before discharge.
5	57	F	8 months	Pollen dust	Loss in weight inability to work weakness for four weeks preceding admission. Three to four acute attacks of asthma daily with poor response to adrenalin. Residual wheeze after adrenalin.	Helium Rebreather with mouthpiece. Helium 71% oxygen 23% $\frac{1}{4}$ to $\frac{1}{2}$ hour treatments two times daily at 2-3 cm pressure for 7 days.	7 days	Residual wheeze after adrenalin completely relieved by helium treatment. After two days patient felt better slept well had better appetite and her chest was clear between attacks. Discharged seven days after admission much improved.

TABLE I—Continued

No	Age	Sex	Duration of Asthmatic History	Probable Etiologic Factors	Clinical State before Treatment	Method Used	Duration of Treatment	Clinical Results
6	61	M	6 years	Bacterial	An attack of grappe six weeks previous was followed by asthma which became progressively worse until patient became taking 1 c.c. adrenalin every hour without relief. Three days before admission, patient coughed up some bronchial crabs. Prognosis very poor. Acute pulmonary emphysema.	Helium hood Helium 70% oxygen 25% 3-4 cm pressure	3 days 3 hours	Patient experienced subjective relief immediately. Response to adrenalin improved until at end of fourth day complete sensitivity to adrenalin was established. Oxygen by face tent was given for three days and patient was discharged 10 days later, taking 1-2 c.c. adrenalin daily.
7	54	M	20 years	Bacterial	Long history of asthma and pulmonary emphysema. For four days before admission patient was in severe intractable asthma receiving no relief from 1 c.c. adrenalin eight times daily. Only slight relief from 4 gr morphine. Respirations very shallow 40 per minute temperature 100.4 pulse 105 very weak. Cyanotic and irrational unable to void. Abdomen distended condition grave. Acute pulmonary emphysema.	Helium hood Oxygen 35%, helium 60% 3 cm pressure for first three days. Oxygen 35% helium 60% 12 hours daily 100% oxygen 12 hours daily for next four days.	7 days	Patient experienced relief immediately but respiratory rate remained over 30 for three days. On the fourth day he was removed from helium for 12 hours with recurrence of symptoms. When placed in hood second time, rales in chest disappeared and patient was removed from apparatus four days later with asthma almost completely gone. Discharged eight days later not having had any morphine or adrenalin in last six days. Completely free from asthma.
8	51	F	8 months	Bacterial?	Given bladder irrigation—that night fever 101 degrees and severe asthma. Been having severe intractable asthma for four days no response to adrenalin. Respirations very labored chest very wheezy.	Helium hood Helium 70% oxygen 25% 3 cm pressure	1 day 22 hours	Patient's breathing very much less labored in helium. At end of one day very much improved reaction to adrenalin. On removal from tent chest was clear but patient had occasional acute attacks. Six weeks later again developed status asthmaticus—nonbund, cyanotic—put in helium O ₂ tent with same dosage for one day 20 hours with marked improvement. She received only 0-0/7 ml adrenalin daily for following week. In hospital at present for work-up regarding epigastric pains.
9	55	M	10 years	Bacterial	Admitted from another hospital after one week's stay for severe asthma. Cyanotic extremely cyanotic at times thrashing in bed. Acute pulmonary emphysema.	Helium hood Helium 73% oxygen 21% 3-4 cm pressure	16 hours	Chest cleared breathing easy—no cyanosis in helium atmosphere. After 16 hours in hood patient was still comatose but with no asthmatic signs. Given oxygen in hood for five days. Rales in abdomen plus tenderness suggested acute cholecystitis. Operation performed with oxygen given continuously. Rectal abscess found (?). Patient died six hours after operation. Post mortem could not be obtained.

TABLE I—Continued

No	Age	Sex	Duration of Asthmatic History	Probable Etiologic Factors	Clinical State before Treatment	Method Used	Duration of Treatment	Clinical Results
10	72	M	?	Bacterial	Four weeks previously had dyspnea after bad cough and cold. Two weeks ago began having continuous asthma unrelieved by adrenalin spray. In hospital five days with continuous asthma. Patient definitely becoming worse.	Helium hood Helium 71% oxygen 23% 3 cm pressure	5 days	Gradual improvement during period of treatment. At end of five days patient given oxygen (50%) by face tent continuously for three days then periodically during day (1 hr TID). Comparatively free from asthma with 1 to 2 injections of adrenalin.
11	52	M	3 years	Bacterial	Two weeks previously had antra irrigated. Since that time asthma worse. For last 24 hours completely refractory to adrenalin. On admission highly nervous man chest very wheezy, squeaks and groans can be heard by ear away from chest.	Helium hood Helium 70% oxygen 25%	1 day 15 hours	For first 18 hours only slight subjective relief experienced. Later complete subjective relief and sensitivity to adrenalin established. On removal from apparatus only very slight residual wheeze remained which disappeared with 1 c.c. adrenalin. Remained in hospital for two and a half weeks after treatment for sinus checkup and skin tests. No adrenalin given or necessary during that period. Discharged very much improved.
12	14	F	2 1/2 months	Bacterial	Cold for three days with cough before admission. Severe asthma 24 hours necessitating adrenalin. In hospital for one and a half weeks when her asthma became worse. Temperature 103.8 degrees. Patient gravely ill.	Helium hood Helium 74% oxygen 20% no pressure	13 hours	Patient's breathing was much easier in helium but she complained of hood. Very uncooperative. Technician unable to give gas under pressure. Removed from hood and placed in oxygen tent for two days. Spiking temperature continued for two weeks and then subsided with relief from asthma. Discharged four weeks after admission very much improved.
13	28	F	4 months	Bacterial	For three weeks, patient had been having increasingly severe asthma. On admission she was getting 5 c.c. of adrenalin daily. She was completely refractory to adrenalin wheezing constantly.	Helium oxygen rebreather helium 75% oxygen 20% 1-2 cm pressure for 1-2 hours daily	3 days	Patient experienced marked subjective relief. Wheeze disappeared on second day and patient had only occasional attack which responded to adrenalin. Two months later, she was readmitted in severe status asthmaticus and dangerously ill. She was treated intermittently for five days about three hours daily and was very much improved. She has had three subsequent admissions with increasingly severe asthma. Her response to helium therapy in each case was very good. In each case, sensitivity to adrenalin was established from within 2 1/2 to 48 hours after helium therapy was instigated. At present she is being treated in the outpatient department with vaccine.

asthma is described before and after treatment. Forty-four patients with severe asthma have been treated, 18 of which were described in earlier reports^{6, 3b}. These patients were admitted to the hospital a total of 54 times for urgent dyspnea. In the accompanying table (table 2) they have been divided into three groups.

TABLE II
Response to Helium-Oxygen Therapy in Forty-Four Patients with Asthma

Classification	No of Admissions to Hospital	Marked Improvement		Moderate Improvement		Little or No Improvement	
		No of Cases	%	No of Cases	%	No of Cases	%
Status asthmaticus	21	14	66	6	28	1	5
Severe more or less continuous asthma	24	10	42	12	50	2	8
Asthma with acute pulmonary emphysema	9	4	44	3	33	2	22
	54	28	52%	21	39%	5	9%

There were 21 admissions for *status asthmaticus*. In this group are included cases in which maximally severe asthma was continuous without any relief resulting from injection of adrenalin. The clinical condition was that of a patient gravely ill. In this group 14 or 66 per cent showed marked improvement incident to the administration of helium-oxygen therapy, generally with positive pressure, 6 or 28 per cent showed moderate improvement, by which we mean that definite objective relief was discerned but that the patient required in addition to other measures a considerable period of time before the asthmatic state was relieved. There was one case in which little or no improvement took place as result of the inhalation of the helium-oxygen mixture for a period of seven hours. In this patient the treatment was temporarily stopped in order to try the effect of intravenous injection of 0.24 gram of aminophyllin in 16 c.c. of normal salt solution. This patient was gravely ill, comatose, deeply under the influence of morphine with a pulse of 140, barely perceptible. During the intravenous injection of aminophyllin the pulse became abruptly impalpable, respiration stopped and the patient died. This patient had been treated four times during the previous two years for *status asthmaticus* of similar severity by the continuous inhalation of helium-oxygen mixtures. Although two to four days of continuous treatment had been necessary at times for complete removal of the asthmatic state, definite clinical relief had ensued within a 24 hour period. It seemed evident that aminophyllin was not suited to this type of advanced *status asthmaticus*.

There were 24 cases of severe, more or less continuous asthma. In this category are included patients who showed some degree of response to

injection of adrenalin but in whom the beneficial broncho-dilating effect was both slight and temporary. In 10 cases or 42 per cent there was marked improvement, in 12 cases or 50 per cent there was moderate improvement, in 2 cases or 8 per cent there was little or no improvement as result of helium-oxygen therapy. It has been emphasized that treatment is directed towards the relief of the chronic wheezing which these patients have, the acute paroxysm is treated by injection of adrenalin when it is effective. More recently, inhalation of large amounts of vaporized adrenalin and neo-synephrin has been used.

There were nine patients in whom severe asthma was accompanied by acute pulmonary emphysema. In these cases the lungs were distended, the respiratory rate was increased and the breathing was shallow. Four showed marked improvement, three moderate improvement and two little or no benefit.

Of the total 54 admissions to the hospital 28 or 56 per cent showed marked improvement, 21 or 42 per cent showed moderate improvement and 5 or 10 per cent showed little or no improvement. In those who showed little benefit, the poor response to helium-oxygen therapy may be attributed either to the severity of the obstruction or to the fact that the slight degree of relief obtained resulted in poor cooperation from the patient.

INHALATION OF THE VAPOR OF NEO-SYNEPHRIN AND ADRENALIN

The introduction of a nebulizer with the vaporization of 1-100 adrenalin by Graeser and Rowe⁹ made it possible for many patients to terminate asthmatic dyspnea without the use of a hypodermic injection. In many instances squeezing the rubber bulb five times terminates a mild or moderate seizure. In other cases slight, temporary or no relief is obtained. Measurement of the amount of adrenalin ordinarily vaporized shows that it is about 0.01 cc. In the more severe cases of asthmatic dyspnea we have found that the vaporization of 1 to 2 cc. of 1-100 adrenalin has afforded relief when the smaller dosage was ineffective. In order to vaporize this amount of adrenalin we have employed the current of air from a compressed air tank or from an oxygen tank at a flow of 8 liters per minute. The lower end of the nebulizer is connected by a rubber tube to the outlet of the oxygen regulator. A small pump capable of maintaining a pressure of 5 to 10 lbs. has also been used.⁹ During the period of 7 to 15 minutes the patient holds the upper end of the nebulizer in his mouth and breathes in the ordinary manner except that it is generally preferable to have the nose closed in order that as much of the vapor as possible be inhaled. We have found no tremor, nervousness or elevation of pulse rate or blood pressure in over 20 patients who inhaled 1.0 cc. of 1-100 adrenalin, although it is entirely probable that patients sensitive to adrenalin may show the characteristic symptoms induced by hypodermic injection of smaller dosage of adrenalin.

tory velocity increased from 105 c c per second before inhalation of neo-synephrin to 286 c c per second after. The inspiratory velocity increased from 265 c c to 464 c c. The vital capacity was more than doubled, increasing from 1100 c c to 2400 c c. This response was not obtained with all patients. In the succeeding graph obtained in a similar patient (graph 2) response to inhalation of 1 c c of 1-100 adrenalin is revealed. It will be observed that a similar increase in inspiratory and expiratory velocity has taken place, but with a very slight increase in vital capacity. The change in the form of the graph is comparable to that produced by neo-synephrin. In most cases, the relief obtained from adrenalin (1-100) is greater than that provided by 1 per cent neo-synephrin.

In patients with pulmonary emphysema we have employed neo-synephrin in 1 or 2 c c doses, night and morning, in order to increase the available functional air by diminishing bronchial obstruction due to congestion or edema. In those cases in which some degree of bronchial spasm is present it has been found valuable to use equal parts of 1-100 adrenalin and 1 per cent neo-synephrin. Frequently relief is obtained within 1 minute of inhalation of the combined drugs but it is our impression that the improvement is more lasting when a full c c of the mixture is employed. In addition to daily inhalation of neo-synephrin morning and evening it has been used before the patient undertakes any unusual exertion. The opening up of the bronchial passageway which is induced in most instances allows for greater exertion with less dyspnea.

INHALATION OF OXYGEN

Inhalation of oxygen-enriched air in concentration of 40 to 50 per cent has been found useful in the treatment of more or less continuous asthmatic dyspnea. The arterial anoxemia is at least partially relieved and there is evidence that a decreased pulmonary ventilation takes place¹³. In a number of graphic studies of acute asthma which we have made, the change in pulmonary ventilation incident to the inhalation of oxygen-enriched air has been either slight or absent. Nevertheless, continuous oxygen therapy for one or two weeks has frequently been followed by cessation of a previously severe protracted asthma.

In chronic hypertrophic pulmonary emphysema a reduced oxygen saturation of the arterial blood is frequently although not always present. Dyspnea on exertion is the earliest characteristic symptom. As the disease progresses these patients become incapacitated and suffer from severe dyspnea at rest. The mechanics of the respiratory act in patients with this disease has been subjected to intensive study¹⁴. The muscles of inspiration are already in the inspiratory position when the act of inspiration begins. An increased amount of work becomes necessary to further distend the lung and a large portion of the air that is inhaled is segregated in peripheral alveolar sacs having an atrophic membrane without an adequate capillary

circulation. As a result partially oxygenated blood is contributed to the aortic stream, and anoxemia and increased CO_2 tensions of the arterial blood are often found. There is a corresponding increase in the alkali reserve. Due to the loss of elasticity of the pulmonary membrane the lungs do not passively collapse and an active expiratory effort is required. As a result of progressive distention of the lungs, the diaphragm is flattened and its contraction pulls the costal margins inward instead of increasing the lung volume at the base of the lung. The upper intercostal muscles, the sternocleido-mastoid and the scalene muscles move the chest upward and in a slightly anterior position. Pulmonary ventilation mainly manifests itself as upper costal respiration, the diaphragm contributing less and less. A large increase in residual air and a decreased vital capacity regularly take place.

The result of these mechanical difficulties and of the pathological state of the pulmonary tissue itself is an impairment of the primary function of the lung, namely, the exchange of the blood gases between the blood and the alveolar air. The lack of correspondence between the degree of anoxemia and the intensity of dyspnea does not make less important the humoral factor as a cause of dyspnea in the emphysematous patient. The sensitiveness to oxygen-want varies considerably in these patients. In 10 patients with severe pulmonary emphysema who frequently experienced dyspnea at rest the inhalation of oxygen increased subjective comfort and diminished the objectively perceived labored breathing in each instance. In all these patients oxygen treatment had been carried on for at least one week and in most of them for considerably longer periods (data to be presented below). In certain cases relief of dyspnea came on immediately, in others after a period of three to five days of inhalation of 40 to 50 per cent oxygen. We have selected two patients who have been treated over a long period of time to illustrate the crucial rôle played by the chemical factor in the cause of dyspnea. The clinical improvement that results from continuous oxygen therapy in this disease has been noted previously,¹⁵ but an adequate recognition of the therapeutic importance of oxygen treatment has not been generally understood. It is our purpose to show that the physiological response to inhalation of oxygen enriched atmospheres reveals that the primary cause of the labored breathing is directly related to the impaired function of the lung in respect to exchange of blood gases. We believe that the emphasis on proprioceptive reflexes as a cause of this type of dyspnea has unduly minimized the humoral chemical influence.

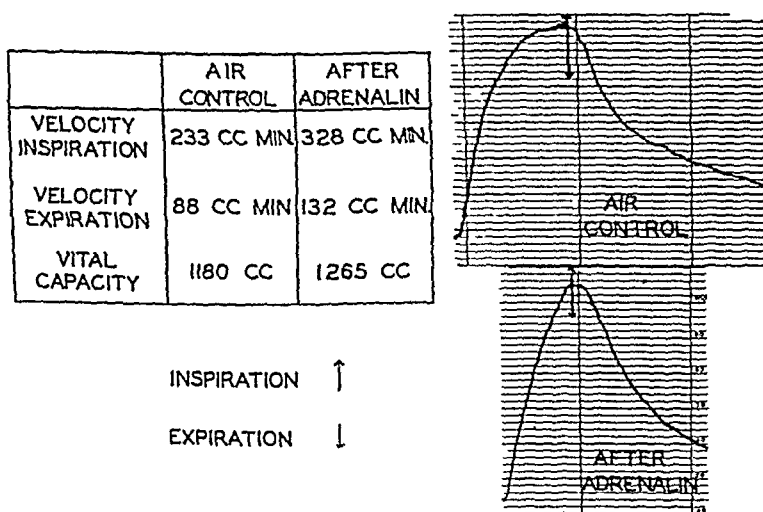
CASE REPORTS

Case 1 Male, aged 74 years. Admission to hospital, September 2, 1937. Present illness. Following a protracted acute bronchitis the patient developed progressively severe dyspnea. During the past year the slightest exertion, such as standing for five minutes, eating, or bathing resulted in severe shortness of breath and heart pounding. After awakening in the morning he had a paroxysmal attack of dyspnea which lasted two to four hours, leaving him exhausted, with a gradual

recovery in the late afternoon. On examination he was a tall, well built man. The dyspnea was characteristically that of a patient with hypertrophic emphysema. There was an elevation of the upper chest with contraction of the neck muscles, the lower costal margin and the infra-sternal region were drawn inward. The lungs were hyper-resonant, breath sounds were prolonged, there were a moderate number of wheezing râles. The heart was not enlarged, the rate was 105 to 120, the blood pressure was 142 systolic and 100 diastolic. Hemoglobin 98 per cent (100 per cent equals 14.9 grams), red blood cells 4 million. Venous pressure 85 with a rise of 4 cm on expiration. Roentgen-ray of the chest showed a moderately flattened diaphragm with an essentially normal cardiac shadow except for a slight widening of the aortic arch, he did not appear cyanotic.

On September 5, 1937, an analysis of the arterial blood gases showed an oxygen saturation of 92.9 per cent and a CO_2 content of 51.9 volumes per cent. At this time numerous graphic records were obtained of the pulmonary ventilation during

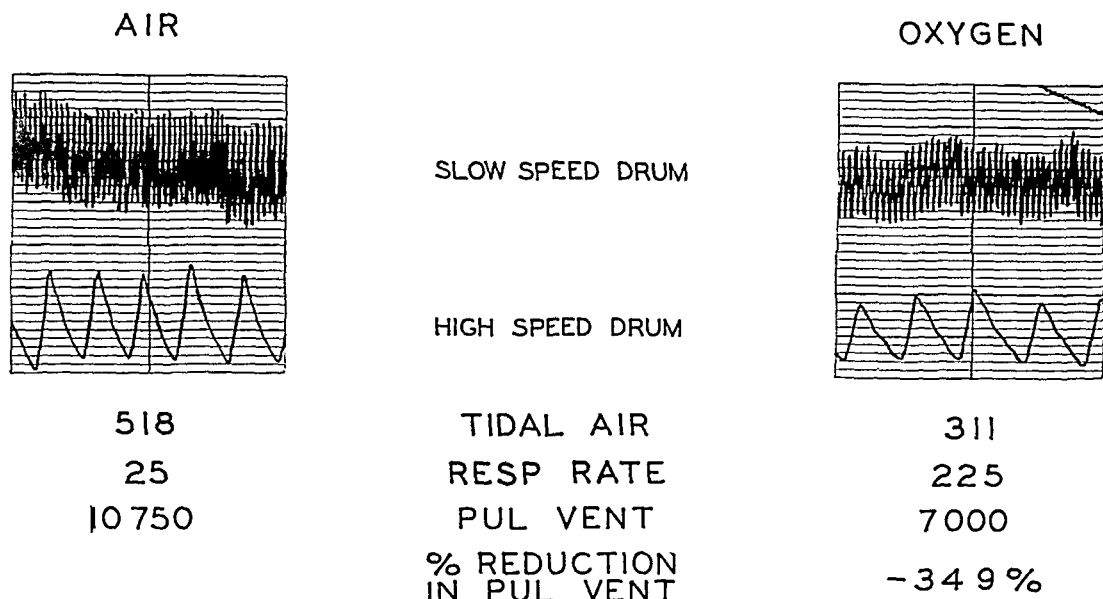
EFFECT OF 1:100 ADRENALIN ON THE VITAL CAPACITY AND RESPIRATORY VELOCITY IN A PATIENT WITH ASTHMA AND ACUTE PULMONARY EMPHYSEMA



GRAPH 2 Effect of 1:100 adrenalin on the vital capacity and respiratory velocity in a patient with asthma and acute pulmonary emphysema

inhalation of air and 100 per cent oxygen. In the accompanying graph (graph 3) a characteristic result is shown. It will be observed that there was an immediate reduction in pulmonary ventilation of 34.9 per cent incident to the inhalation of oxygen, due in part to a fall in respiratory rate from 25 to 22.5 and in part to a decrease in the volume of the tidal air from 418 to 211 cc. It is noteworthy that this marked decrease in the ventilatory requirement took place in the presence of a very slight lowering of the arterial oxygen saturation. There was definite consciousness of relief of dyspnea. Oxygen treatment begun at this time, consisted of residence in a portable oxygen room at his home for approximately 17 hours during the 24, including, for the most part, the evening, night and early morning. There were five periods in which for 10 days to 3 weeks the patient resided continuously in the oxygen chamber at the hospital. Up to February 15, 1938 the oxygen concentration employed was 50 per cent, from then on up to the date of writing (March 25, 1938) it has been between 37 and 40 per cent.

IMMEDIATE REDUCTION IN PULMONARY VENTILATION, WHEN BREATHING OXYGEN, IN A PATIENT WITH PULMONARY EMPHYSEMA



GRAPH 3 Immediate reduction in pulmonary ventilation, when breathing oxygen, in a patient with pulmonary emphysema

During the hospital admissions the patient was removed from the oxygen room for periods of 1 to 17 hours in order to test his ventilatory response to inhalation of air and 100 per cent oxygen. The results on the pulmonary ventilation are shown in the accompanying table (table 3). In 14 tests during a period of six months, a

TABLE III

Immediate Reduction in Pulmonary Ventilation on Inhaling 100% Oxygen, in a Patient with Pulmonary Emphysema, during a Course of Oxygen Treatment

Date	Tidal Air	Air 100% O	Resp Air	Rate 100% O	Pulmonary Ventilation Liters per min		% Reduction in Pulm Vent due to Oxygen	Vital Capacity	Relation to Course of Oxygen Treatment
					Air	100% O ₂			
9-3-37	390	216	29.5	30	11500	6480	43.7		Before O treatment
9-5-37	304	270	26.5	26.5	8660	7180	17.1		
9-8-37	419	375	25	25	10470	9380	10.4		O treatment 3 days
9-14-37	363	305	25	24.5	9080	7470	17.7	1430	9
10-26-37	352	296	25.5	21	8970	6220	30.7	1630	51
10-29-37	358	265	25	23	8940	6090	31.9		54
11-24-37	518	311	25	22.5	10750	7000	34.9	1490	80
12-22-37	370	320	27	24	9980	7680	23.0	1535	108
12-27-37	360	285	24	20.5	8640	5840	32.4		113
1-17-38	320	188	24	23	7690	4320	43.8	1660	137
1-20-38	369	286	24	22	8860	6290	29.0	1880	140
1-30-38	408	321	23	21	9370	6740	28.1	1680	150
2-4-38					9290			1980	155
3-4-38					9810	7432	21.5		183
3-10-38					7860			2125	189
3-23-38	415	338	19.5	19	8100	6420	20.7		202

decrease in pulmonary ventilation of from 20 to 40 per cent took place when 100 per cent oxygen was substituted for air, in each instance with an immediate consciousness of alleviation of dyspnea. When the patient breathed a 37 per cent oxygen atmosphere the immediate reduction in pulmonary ventilation was found to be 17 per cent. On January 17, 1938 the patient had been in air for six hours prior to the test. At that time his arterial oxygen saturation was 98.8 per cent. The measurement of his ventilation even in the absence of arterial anoxemia showed a fall of 43.8 per cent. The finding, therefore, of a normal or slightly lowered arterial oxygen saturation in a dyspneic patient does not warrant the assumption that the oxygen tension in the blood is not causally related to dyspnea. It is evident from the numerous observations on this patient that the excessive resting pulmonary ventilation, although it produced dyspnea, maintained a normal or nearly normal oxygen saturation of the arterial blood.

The vital capacity of this patient at the beginning of treatment was 1430 cc. At the date of writing (March 13, 1938) the vital capacity is 2125 cc, this is further increased after inhalation of 2 cc of 1 per cent neo-synephrin to 2300 cc. It may be mentioned at this point that two weeks after initiation of oxygen treatment all râles cleared in the lungs and the patient has not been conscious of a wheeze at any time.

The arterial oxygen saturation when the patient was in an atmosphere of 40-50 per cent oxygen was raised above the normal range, indicating that the hemoglobin was fully saturated and that there was additional oxygen in physical solution in the plasma (table 4). The carbon dioxide content of the arterial blood was 51.9 volumes per cent in air, when his pulmonary ventilation was much increased. After four months of intermittent oxygen treatment (17 hours in 24) the arterial CO₂ content in air was 63.1 volumes per cent. During a period of continuous residence in atmosphere of 50 per cent oxygen in the hospital from January 17 to February 1, 1938 the CO₂ content rose from 63.1 volumes per cent to 78.6 volumes per cent on January 21 and then subsequently declined on January 28 to 65.8 volumes per cent. On February 1 the CO₂ content was 66.9 volumes per cent. On March 23, 1938, the arterial CO₂ content breathing air was 59.8 volumes per cent. The alteration in CO₂ content due to oxygen treatment will be discussed later (Table 4).

After six months of oxygen treatment, for the most part for a period of approximately 17 hours a day, the patient presents a clinical state decidedly better

TABLE IV
Blood Cases in a Patient with Pulmonary Emphysema during Oxygen Treatment

Date	Oxygen Content Vol %	Oxygen Capacity Vol %	Oxygen Saturation %	CO ₂ Content Vol %	Remarks
9-3-37	20.15	21.7	92.9	51.9	Before oxygen treatment
9-22-37	16.9	18.6	91.0	61.6	Breathing air
9-22-37	19.3	19.6	99.0	63.8	Breathing 50% oxygen
1-17-38	16.6	16.8	98.8	63.1	Breathing air, after 137 days oxygen treatment
1-18-38	18.4	17.9	102.8	69.9	Breathing 50% oxygen
1-21-38	17.8	17.55	101.5	78.6	Breathing 50% oxygen, after 141 days oxygen treatment
1-28-38	17.45	16.95	102.9	65.8	Breathing 40% oxygen, after 148 days oxygen treatment
2-1-38		17.1		66.95	Breathing 40% oxygen, after 152 days oxygen treatment
3-23-38	15.55	16.9	92.0	59.85	Breathing air, after 202 days oxygen treatment

than that prior to treatment. He has no morning attacks of dyspnea. The inhalation of 0.5 cc of 1-100 adrenalin followed two hours later by the inhalation of 1 cc of neo-synephrin enables him to bathe, and to get dressed without uncomfortable dyspnea. Although a wheel chair is made use of to cover any extended distance he is able to walk 60 steps to and from the dining room or into the living room without undue puffing. It is also possible for him to go to a hotel for dinner and to entertain friends. His pulse rate has decreased from a range of 105-120 to a range of 80-100. His most recent test showed a pulmonary ventilation of 81 liters per minute in air, which is considerably less than his pulmonary ventilation before oxygen treatment was begun. There is a marked decrease in infra-sternal and lower intercostal retraction during the residence in the oxygen-enriched atmosphere.

Oxygen treatment in this patient has resulted in a marked relief of subjective dyspnea and a distinct improvement in the function of the respiratory system. It seems likely that the progress of the disease has been retarded.*

Case 2 Male, aged 59. Admission to hospital February 20, 1936. Present illness. The patient has had chronic dry hacking cough for 40 years. Seven years ago he began to have attacks of definite bronchitis lasting two to three days, occurring two to three times a year, accompanied by fever and sputum. Following removal of his gall-bladder at that time and the development of a ventral hernia, dyspnea on exertion began. A gradual increase of severity of dyspnea took place so that during the past year it has become impossible for him to walk 40 yards. In addition, he developed paroxysms of extremely labored breathing which occurred at night without relation to exertion. On two occasions he inhaled 50 per cent oxygen for one to two hours without relief. At the time of our first observation, he had an almost continuous hacking cough, the slightest effort caused extreme dyspnea, he was weak and depressed. *On examination*, he was a thin, poorly developed man of 56 years, bending forward, whether standing or sitting, markedly dyspneic with upper costal respiration, inspiratory contraction of the neck muscles and retraction of the lower intercostal and substernal regions. There was no cyanosis. The lungs were hyperresonant, breath sound feeble and prolonged without râles. Roentgen-ray of the chest showed a markedly flattened diaphragm with a long narrow heart. The pulse rate was 80, the blood pressure was 120 systolic and 70 diastolic. Venous pressure 40. The lung fields showed evidence of fibrotic change especially in the lower regions. An abdominal binder had occasionally been worn without noticeable change in his breathing, and without subjective relief.

The patient was too dyspneic to measure his pulmonary ventilation with a mouthpiece and nose clip, a Benedict helmet respiration apparatus¹⁰ was therefore used which gives a pulmonary ventilation about 15 per cent less than that obtained with the mouthpiece due to an unrecorded fluctuation in the rubber collar during the respiratory cycle. Under these circumstances the pulmonary ventilation in air was 5.7 liters and in 100 per cent oxygen 4.8 liters per minute. The decrease in pulmonary ventilation was due entirely to a lowering of the tidal air from 309 to 209 cc.

In a later admission (December 23, 1936) his arterial oxygen saturation in air was 96.7 per cent, the CO₂ content was 66.3 volumes per cent. On the following day breathing 40 per cent oxygen in the oxygen room the arterial oxygen saturation was 102.7 per cent, the CO₂ content 71.8 volumes per cent. The next day the CO₂ content was 74.1 volumes per cent and four days later with the same oxygen concentration in the room 70.8 volumes per cent. During the period of residence in the oxygen room the patient had only a transient sensation of dyspnea, he only infre-

* At the time proof was received, September 4, 1938, one year after institution of oxygen treatment and inhalation of adrenalin-neo-synephrin vapor, the patient continues to maintain the improvement described, both clinically and in respect to measurements of pulmonary function.

quently felt the inclination to use inhalations of 1-100 adrenalin and he had no severe paroxysms of dyspnea. On his return home his dyspnea again increased, despite nasal oxygen at three liters per minute, and was only relieved completely in an atmosphere of 100 per cent oxygen. At night nasal oxygen was successful in per-

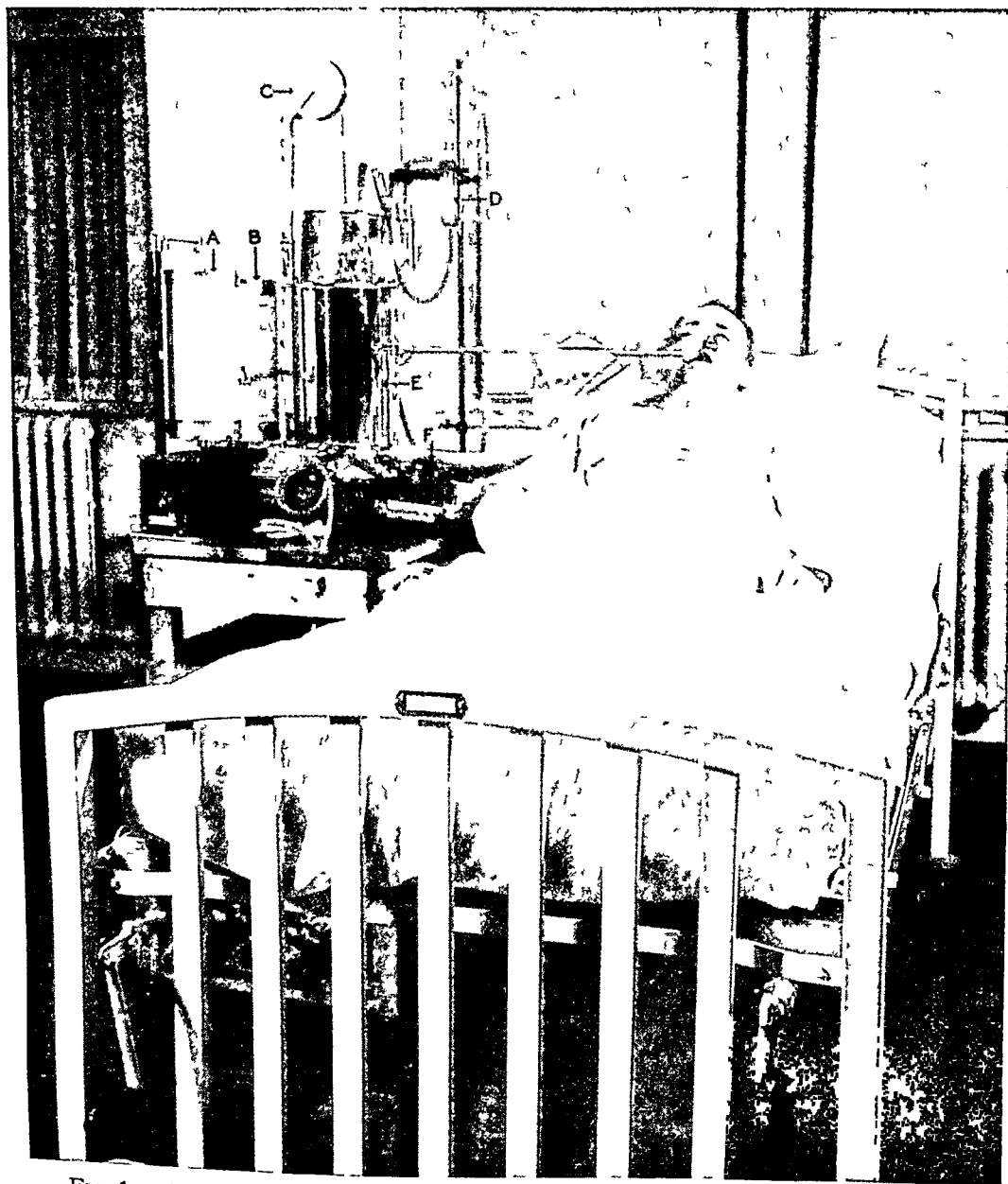


Fig 1 A High speed drum B Standard recording drum C Reichert counter D Levelling device with automatic oxygen administration E Spirometer of basal metabolism apparatus F Motor blower unit with rheostat

mitting sleep without continual coughing or dyspnea. Paroxysmal attacks of dyspnea were relieved by inhalation of 1-100 adrenalin.

During the first year of oxygen treatment the patient was able to do four to five hours legal work at his office each day. During the second year his failure to improve sufficiently to restore his customary earning power contributed largely to an

increasing depression. Even during period when his dyspnea was largely controlled by continuous oxygen therapy at the hospital, he retained a gloomy outlook based on the realization of his loss of earning power and, finally, on his inability to afford adequate oxygen therapy at home.

The intermittent employment of oxygen therapy in this patient has prolonged life over a two year period. The paroxysmal dyspnea, the cough and the more continuous labored breathing largely disappeared in continuous residence in 40 to 50 per cent oxygen in a hospital oxygen room. These symptoms recurred at home and are now only partially relieved by nasal oxygen plus inhalations of adrenalin and neo-synephrin. The depression which the patient had at the onset of treatment was considerably improved during the first year in which he was able to work part of the day. If the economic situation in which he finds himself were less precarious than it is, his depression would undoubtedly be materially modified. He is unable to do without nasal oxygen, three liters per minute, although this is inadequate to prevent dyspnea. Cessation of oxygen treatment, however, results in return of cough and severe dyspnea. This patient illustrates the importance of considering the factor of expense in arranging for long continued treatment of a patient with emphysema. In individuals who are not able to afford prolonged oxygen treatment the decision to provide temporary relief should be seriously weighed. Removal from an oxygen-enriched atmosphere may result in a recurrence of dyspnea, cough and depression, which may become difficult to handle.

COMMENT ON OXYGEN TREATMENT AND PATHOLOGICAL PHYSIOLOGY IN PATIENTS WITH PULMONARY EMPHYSEMA

Graphic records of the pulmonary ventilation in patients with pulmonary emphysema have been used to elucidate certain aspects of the pathological physiology of the disease and to serve as a basis for treatment. In the two cases selected for detailed description the resting pulmonary ventilation was markedly increased above normal. In each instance, the inhalation of 100 per cent oxygen for a five minute test period resulted in a substantial lowering of the total pulmonary ventilation and in partial relief of subjective dyspnea. Residence in an oxygen chamber with an oxygen concentration of 40 to 50 per cent was followed by complete relief of dyspnea in one case at the end of four days and in the other after 24 hours treatment. Determination of the arterial oxygen saturation revealed in both instances a slightly lowered oxygen saturation. While the patient was breathing 50 per cent oxygen the arterial oxygen saturation was increased above the usual normal range. It may be pointed out, therefore, that a normal saturation of the arterial blood with oxygen cannot be used as an argument that dyspnea is not causally related to the oxygen tension of the blood and tissues. In the two patients studied, one over a period of two years and the other for six months, it was clear that an excessive pulmonary ventilation was maintained at the expense of subjective dyspnea, but with the result that a normal or nearly normal oxygen saturation of the arterial blood was achieved. Since complete freedom from dyspnea took place in an oxygen enriched atmosphere, it is difficult to avoid the conclusion that their pulmonary ventilation in air had been increased to avert anoxemia. Expressed from a more objective point of view, these patients consistently revealed a

sensitiveness to the oxygen tension in the atmosphere which determined the quantity of air moved in and out of the lungs, increasing the oxygen supply was followed by relief of dyspnea, decreasing the oxygen supply resulted in recurrence of dyspnea

Proprioceptive reflexes from the lungs and the chest wall are responsible for the transmission intracerebrally of the sensation of dyspnea. The mechanical difficulties of breathing which are in large part created as a result of chronic over-distention of the lungs, bring about a patho-physiological state in which the patient's resting pulmonary ventilation is nearer to his maximal pulmonary ventilation than is the case in the normal individual. The degree of dyspnea in chronic pulmonary disease has been said to vary directly with the extent to which the pulmonary ventilation approaches the maximal pulmonary ventilation or to the vital capacity¹⁴. In the patients which we have studied this correlation undoubtedly exists but we have been particularly impressed with the rôle played by the primary function of the lung, namely, the transmission of oxygen into the arterial blood. The increased respiratory effort which is perceived as labored breathing tends to maintain a constancy of the internal environment in respect to tissue oxygen supply.

In patients with chronic pulmonary disease treated over relatively long periods of time with oxygen-enriched atmospheres, a characteristic rise in the carbon dioxide content of the arterial blood takes place. In previous reports by Richards and the author,¹⁷ this has been explained as a mechanism which allows a greater elimination of CO_2 per breath in the presence of a decreased pulmonary ventilation initially made possible by an increase in the oxygen tension of the arterial blood. A progressive rise in arterial CO_2 content has been observed in patients with chronic heart disease, occurring in conjunction with a lowering of the total pulmonary ventilation. The elevation in arterial CO_2 content may reach a maximum in some cases in two to three weeks and then gradually fall toward the normal level even during continuous residence in an oxygen-enriched atmosphere. This type of response has been characteristic of patients who have shown clinical improvement in respect to pulmonary pathology and function. In patients with chronic pulmonary disease in whom clinical improvement has persisted after removal from an oxygen environment a similar response has been observed, namely, a decline in CO_2 content following an initial rise. Thus, the first case reported in this paper had a substantial lowering of arterial CO_2 content following a preliminary rise, and clinically experienced marked benefit, the second case showed only a slight fall in arterial CO_2 content from his maximal rise, and clinically his symptoms recurred after removal from an oxygen environment.

In the accompanying table (table 5) the maximal rise in arterial CO_2 content in 10 patients with chronic pulmonary disease treated with oxygen is recorded. In Case 2 a negligible increase in CO_2 content was found. In this patient despite active tuberculosis there was little or no impairment

of respiratory function in respect to absorption of oxygen. In seven of the remaining patients, the CO_2 content of the arterial blood rose 20 or more volumes per cent. In Case 3 an arterial CO_2 content of 132.1 volumes per cent was found after six months residence in an oxygen enriched atmosphere. In this patient an advancing pulmonary fibrosis, associated with infection or carcinoma, progressively impaired pulmonary function in respect to the absorption of oxygen. Although she was at first comfortable in an atmosphere of 40 per cent oxygen, she later required 60 per cent oxygen. Her vital capacity at that time appeared to be no greater than 250 c.c. It may be concluded that a progressive elevation in the carbon

TABLE V

Maximal Rise in Arterial CO_2 Content in 10 Patients with Chronic Pulmonary Disease Treated with Oxygen

Case Diagnosis No	Arterial Oxygen Saturation %		Arterial CO_2 Content		Remarks
	before	after	before	after	
	Treat-ment	Treat-ment	Treat-ment	Treat-ment	
1 Chronic pulmonary tuberculosis	88%	93%	54.9	73.5	Patient resided in oxygen chamber 50% oxygen for 43 days at time of second test
2 Chronic pulmonary tuberculosis	97%	95%	49.0	51.0	Patient resided in oxygen chamber 50% oxygen 7 days at time of second test
3 Advanced pulmonary fibrosis		89%		132.1	Test obtained after 6 months residence in oxygen chamber, oxygen concentration between 50-60%
4 Advanced pulmonary fibrosis	70%	90%	38.4	69.7	Patient resided in oxygen chamber at 50% oxygen 4 days at time of test
5 Pulmonary emphysema	92.9%	101.5%	51.9	78.6	Six months oxygen treatment 17 hours daily Two weeks before test continuous residence in 50% oxygen
6 Pulmonary emphysema	68.09%	93.0%	62.6	91.7	1 month in 50% oxygen
7 Pulmonary fibrosis	86.0%	96.0%	66.0	84.2	6 days in 45% oxygen
8 Pulmonary fibrosis and emphysema	96.7%	102.7%	66.3	74.1	6 days in 40% oxygen
9 Chronic pulmonary tuberculosis and pulmonary fibrosis	88.0%	100.0%	57.0	77.0	35 days in 45% oxygen
10 Pulmonary fibrosis and emphysema	93.0%	97%	60.0	66.2	5 days at 26% oxygen

dioxide content of the arterial blood during continuous oxygen treatment indicates a failure of improvement both in pulmonary pathology and function, whereas a fall in arterial CO_2 content following a previous rise is of favorable prognostic import and indicates a likelihood of betterment in pulmonary function and clinical improvement as result of oxygen treatment.

The inhalation of 100 per cent oxygen does not always show an immediate fall in pulmonary ventilation in patients with pulmonary emphysema. This response is sometimes obscured by the factor of respiratory obstruction due to spasm of the bronchial musculature and the congestion and edema of the bronchial wall. When bronchial obstruction is removed by inhalation of 1-100 adrenalin, 1 per cent neo-synephrin or a combination of both,

the patient may then show a marked decrease in pulmonary ventilation due to inhalation of 100 per cent oxygen, although little or no effect was produced by oxygen prior to inhalation of these substances. Thus, in a patient with severe pulmonary fibrosis who is now experiencing considerable benefit from continuous oxygen therapy, the pulmonary ventilation test at first showed very slight alteration when oxygen was substituted for air. However, when the factor of bronchial obstruction was removed by inhalation of adrenalin and neo-synephrin a marked diminution in the amount of air breathed per minute took place. In the accompanying table (table 6) the pulmonary ventilation test is recorded before and after inhalation of adrenalin and neo-synephrin. In six out of eight tests the diminution in pulmonary ventilation when 100 per cent oxygen was breathed was much

TABLE VI

Reduction in Pulmonary Ventilation When Oxygen Is Substituted for Air in a Patient with Pulmonary Emphysema before and after Inhalation of Vaporized Adrenalin and Neo-Synephrin

Inhalent	BEFORE INHALENT			AFTER INHALENT		
	Pul Vent Air	Pul Vent Oxygen	% Reduction in Pul Vent	Pul Vent Air	Pul Vent Oxygen	% Reduction in Pul Vent
	c c per min			c c per min		
3 cc Neo synephrin						
1 cc 1 100 adrenalin	10200	9330	8 7	10900	8560	21 5
3 cc Neo-synephrin						
1 5 cc 1 100 adren	11300	9200	18 6	15460	9120	41 0
3 cc Neo synephrin						
1 cc 1 100 adrenalin	8820	8295	6 0	10850	6600	39 2
3 cc Neo synephrin	7110	8120	10 9	8300	7950	5 4
2 cc Neo-synephrin	11400	9160	19 7	11500	8380	27 1
2 cc Neo synephrin	10930	9010	17 7	9500	8210	13 6
1 cc 1 100 adrenalin	10070	9550	5 2	10800	8700	19 4
1 cc 1 100 adrenalin	11100	10110	8 9	11400	8720	23 5

greater after inhalation of adrenalin and neo-synephrin. Thus, in the third test, inhalation of 100 per cent oxygen was followed by a 6 per cent reduction in pulmonary ventilation, after inhalation of 3 c c of neo-synephrin and 1 c c of 1-100 adrenalin there was a 39 per cent reduction in pulmonary ventilation when 100 per cent oxygen was breathed. It is evident, therefore, that the factor of respiratory obstruction should be counteracted by inhaling the vapor of adrenalin and neo-synephrin before it is concluded that 100 per cent oxygen does not lower the total pulmonary ventilation. It should also be remembered that the patient with chronic pulmonary disease may show a gradual decrease in labored breathing in a period of three to five days even when the pulmonary ventilation test shows no immediate decrease in the volume of air breathed with oxygen.

The importance of the chemical factor in the etiology of dyspnea in patients with pulmonary emphysema is illustrated in the following experiment performed on the first case reported above. The pulmonary ventilation was determined while he was breathing air. Arterial blood was taken for measurement of the blood gases and the pH. The patient then inhaled 100 per cent oxygen, and arterial blood was drawn 90 seconds later. The data are recorded in the accompanying table (table 7). It will be

TABLE VII

Pulmonary Ventilation and Blood Gases of a Patient with Pulmonary Emphysema, before and after Relief of Dyspnea Due to Inhalation of 100% Oxygen for 90 Seconds

Breathing Air		After Breathing 100% Oxygen for 90 Sec
8100 c c	Pulmonary ventilation	6420 c c
92.0%	Arterial oxygen sat	101.2%
59.85 Vol %	CO ₂ content	60.75 Vol %
57.2 Vol % *	CO ₂ capacity	57.35 Vol % †
7.41	pH	7.40

* Equilibrated at 43.7 mm Hg pressure CO₂.

† Equilibrated at 45.2 mm Hg pressure CO₂.

observed that an immediate fall in pulmonary ventilation from 8100 to 6420 c c took place coincident with a rise in arterial oxygen saturation from 92.0 to 101.2 per cent. The CO₂ content of the arterial blood rose slightly and the pH changed merely from 7.41 to 7.40. A more comprehensive study of variations in CO₂ tensions and in pH of the arterial blood as they are affected by oxygen treatment has been made by D. W. Richards,¹⁸ but it is sufficient for our present purpose to indicate that the change in oxygen saturation of the arterial blood was essentially responsible for the decline in pulmonary ventilation and the concomitant alleviation of dyspnea. The time interval involved, namely 90 seconds, was too brief to allow any change to take place in the mechanical difficulties of breathing. Although we are aware that relief of labored breathing does not take place as promptly as it did in this instance in all cases of pulmonary emphysema, it is nevertheless our belief that continuous residence over a period of three to six days in an oxygen enriched atmosphere will result in a marked decrease of labored breathing in most instances.

POSITIVE PRESSURE BREATHING

Atmospheres under small increases of pressure such as 2 to 5 cm of water have been employed in inhalational therapy in order to diminish the inspiratory effort and to facilitate the egress of air during expiration by diminishing expiratory constriction of the intra-thoracic bronchi and bronchioles^{19, 20}. A study has been made in collaboration with Dr. Paul Swenson in which the size of the smaller bronchi has been measured before and after positive pressure was used. (A full report will be published elsewhere.)

Patients during an attack of asthma were injected intratracheally with lipiodol. Roentgenograms of the chest were taken during ordinary res-

piration and during the inhalation of an under 4 to 8 cm positive pressure. It was shown that the lumen of an isolated bronchus during positive pressure respiration did not constrict during expiration as much as it did during respiration without positive pressure. In some cases the diameter of the bronchus was 25 per cent larger with positive pressure breathing.

Based on the clinical use of positive pressure respiration, an exercise has been suggested to patients which consists in pursing the lips during expiration, this creates a positive pressure which is deflected backward into the bronchial tree. Inspiration is conducted as usual and expiration with the lips narrowed to maintain a resistance equivalent to that created by breathing outward through a tube $\frac{1}{8}$ of an inch in diameter. This exercise pursued for two or three minutes at a time will clear up some types of continuous mild or moderate wheezing, witnessed both by subjective relief as well as the clearing of râles during expiration. In the patient with pulmonary emphysema it will also be found that the milder degrees of dyspnea are lessened by this exercise.

Livingstone¹⁹ and others²⁰ have reported marked improvement from respiratory exercises. It is obvious that the ordinary breathing exercises in which the object is to inspire as deeply as possible are useless. When the asthmatic patient breathes deeply his respiration seems almost entirely upper thoracic. The lower part of the chest is already largely expanded and if it moves at all shows inward retraction. The diaphragm is thus of little or no value. The breathing exercises designed by Livingstone attempt to teach the patient to use the lower part of the chest and the diaphragm more, and to empty the lungs more completely. The patient takes a quiet inspiration followed by a long expiration, with the lips partially closed to make an F sound. Expiration is assisted by pressure with the hands on the lower part of the chest. Our own experience is limited to the simple exercise described above, namely, exhaling with the lips partially closed which in the chronic asthmatic patient and the patient with pulmonary emphysema has been found specially valuable, and which may be pursued as often as needed.

METHODS OF INHALATIONAL THERAPY

The recent advances in the methods of inhalational therapy have been subjected to a detailed review²¹. It should be emphasized that no one method is suitable for all patients and that the patient should generally be given the choice as to which is more comfortable for him, especially when oxygen treatment is administered at home at intervals over long periods of time. The introduction of the face tent or face mask by Argyll Campbell²² has made possible the administration of relatively high concentrations of oxygen without more elaborate apparatus. Our own modifications of this apparatus have included recently the use of the so-called "oxyator" which works on the principle of the Bunsen burner and which sucks in a small increment of air as the oxygen passes through it. The additional flow of

this oxygen enriched atmosphere makes for increased comfort and for lower concentration of carbon dioxide in the inspired air. In the accompanying table (table 8) it will be seen that the oxygen per cent in the inspired air increased to 42 to 52 per cent as the oxygen flow is increased from 6 liters per minute to 10 liters per minute and that the CO₂ concentration is lowered from 0.9 to 0.50 per cent. This carbon dioxide concentration corresponds to that generally present in an oxygen tent as it is ordinarily administered. With higher pulmonary ventilations the per cent of carbon dioxide and of oxygen falls slightly. It is also true that haphazard employment of the face tent will not achieve as good results as are here reported. This also applies to the management of more complicated apparatus. It is our opinion, based on experimental evidence and on clinical usage, that the face tent is of considerable value in many instances²³ although it must be ad-

TABLE VIII

The Concentration of Oxygen and Carbon Dioxide in the Inspired Air When the Face Mask Is Used at Flows between 6 and 10 Liters per Minute

Oxygen Flow Liters/min	20 Respirations/min				30 Respirations/min		
	Alveolar Oxygen per cent	Alveolar CO ₂ per cent	Calculated Oxygen per cent in inspired air	CO ₂ per cent in inspired air determined from gas sample during inspiration	Alveolar Oxygen per cent	Alveolar CO ₂ per cent	Calculated Oxygen per cent in inspired air
6	36.3	5.7	42	0.95	34.2	5.8	40
8	41.3	5.7	47	0.85	39.8	5.7	45.5
10	46.1	5.9	52	0.50	45.4	5.6	51.0

Alveolar CO₂ Breathing air
Alveolar O₂ Breathing air

5.1
14.8

mitted that it rarely provides the comfort of a well ventilated oxygen tent with completely transparent plexiglass covering.

The question of expense in relation to long continued oxygen therapy merits consideration. The cost of oxygen varies at least 100 per cent depending upon the quantity of oxygen used. For patients of moderate means it is almost always possible to obtain a lower than standard rate from one of the larger companies. It is frequently desirable for the patient to purchase his own equipment, such as regulator, nasal catheter, or face tent. Depending upon the number of hours used per day the expense of oxygen treatment can then be accurately calculated and the patient or his family be informed of the possibility that in cases of pulmonary emphysema it is likely that the patient will require for the rest of his life a continuance of oxygen treatment, if his dyspnea is to be modified. Fur-

thermore, during periods of exacerbation of his illness such as might be provoked by acute respiratory infection more oxygen might become necessary

For many patients intermittent oxygen therapy is preferable because of its simplicity, low cost and freedom from ultimate dependence on oxygen as a method of maintaining life. Periods of treatment ranging from one-half hour to one hour, two or three times in the day are of considerable help in diminishing pulmonary distention and in relieving distress. The nasal catheter with a flow of 6 liters per minute will provide an oxygen concentration of approximately 37 per cent in the inspired air, the face tent with a flow of 10 liters per minute will ensure an oxygen concentration of 50 per cent if used intelligently.

When a program of continuous oxygen therapy is decided upon, it is generally advisable to expose the patient to a gradually increasing oxygen concentration rather than suddenly to place him in an atmospheric environment which contains 50 per cent oxygen, a suggestion made to us by Palmer²⁴. Patients who have suffered from chronic oxygen deficiency, especially in breathless subjects, may become irrational or stuporous when they are abruptly given a high oxygen atmosphere. The sudden change in the tension of oxygen to which the brain cells are exposed appears to interfere remarkably with their function, a circumstance which Richards and the author have noted also in the treatment of patients with chronic heart disease^{15c, d, e}. The mental state may manifest itself as stupor, coma, excited delirium or depression in severe cases but it is characteristic that after a period of two to six days a rational state returns, generally with a feeling of well-being. The feeling of cheerfulness which terminates the prior upset may be paralleled by more optimistic views of his affairs outside the realm of illness²⁵. This reaction, which is an interesting example of the effect of biology on psychology, does not occur except in those patients who have suffered from long-standing oxygen-want. Nevertheless, it should be borne in mind during the initiation of treatment, for patients in whom such a reaction is suspected, oxygen may be administered at a concentration of 30 per cent the first day, increasing the concentration 5 per cent each day until 50 per cent concentration is obtained. The length of time which the patient with pulmonary emphysema should be treated with 50 per cent oxygen depends on the individual patient, some of the factors involved have been mentioned previously. Whether the duration is 2 or 5 weeks, the important consideration is gradual reduction of the oxygen concentration administered. Fully two weeks should be utilized in gradually returning the patient to atmospheric air. In all of these cases, it is desirable to substitute intermittent oxygen therapy following the course of continuous treatment. In those patients who have the facilities for it, as much as 17 hours a day may be spent in an oxygen enriched atmosphere. In others, two to three half-hour periods during the 24 hours may be more feasible.

The method of administration of helium-oxygen mixtures has been described²¹ It may be mentioned here that the U S Government has recently released helium for medical purposes at a moderate cost In the absence of the special apparatus designed for its use, a tent or a face mask may be employed provided flows of 25 to 30 liters per minute are maintained The administration of helium is more apt to be successful when a trained internist, anesthetist or an expert technician is in immediate charge of the treatment The relief of obstructive dyspnea in cases in which edematous infiltration of the bronchial walls is extensive requires time, attention and special experience

SUMMARY

Graphic recording of the pulmonary ventilation has been employed as a quantitative and qualitative test of respiratory function in patients with asthma and pulmonary emphysema The effectiveness of physiologically directed therapy has been determined by this test which measures the response of the patient in terms of the total quantity of air breathed per minute as well as the velocity of air movement during the respiratory cycle

The sensation of dyspnea in patients with asthma may be mainly attributed to an increased effort on the part of the respiratory musculature to ventilate the lungs in the presence of narrowing of the smaller bronchi The inhalation of a helium-oxygen mixture makes possible a more normal velocity of gas movement with diminished respiratory effort This physiological advantage in breathing helium-oxygen mixtures has been employed in the treatment of patients with severe asthma, *status asthmaticus* and asthma complicated by acute pulmonary emphysema Of a total of 54 admissions to the hospital 28 patients showed marked improvement that could be specifically attributed to the use of helium Twenty-one showed moderate improvement, or a combined percentage of 91 per cent Five patients or 9 per cent showed little or no benefit from helium-oxygen therapy

In chronic pulmonary emphysema the continuous inhalation of oxygen enriched air relieves the sensation of dyspnea in most instances Two patients are reported in detail who suffered from severe dyspnea at rest The oxygen saturation of the arterial blood was at or near the normal level in each case, however, an immediate and progressive fall in pulmonary ventilation resulted from the inhalation of high concentrations of oxygen, accompanied by relief of dyspnea In one patient, a more permanent benefit took place during a period of six months intermittent oxygen treatment This patient showed a preliminary rise in arterial CO_2 content followed by a fall during a test period of continuous residence in an oxygen enriched atmosphere In the other patient, clinical improvement persisted only during the course of oxygen treatment over a period of two years In the latter case only a slight decrease in arterial CO_2 content followed the previous rise The mechanism of the rise in the carbon dioxide content of

arterial blood is discussed in 10 patients with chronic pulmonary disease treated with oxygen over relatively long periods of time. The humoral (or chemical) factor in the causation of the dyspnea of pulmonary emphysema is emphasized by the results in cases of chronic pulmonary disease treated by oxygen enriched atmospheres.

The inhalation of vaporized adrenalin in larger amounts than have hitherto been employed has been found markedly helpful in the treatment of patients with severe asthma and pulmonary emphysema. The inhalation of vaporized neo-synephrin in relatively large doses is reported as an additional helpful agent in these conditions, as a result of unpublished studies by D. W. Richards and the author. Routine use of adrenalin and neo-synephrin mixtures has been found clinically beneficial in the treatment of pulmonary emphysema. Graphic records of the pulmonary ventilation reveal, as a result of inhalation of these agents, an increased velocity of air movement, especially marked in the expiratory cycle, and an increase in vital capacity.

A simple breathing exercise consisting of pursing the lips during expiration is suggested for patients with asthma and pulmonary emphysema. The positive pressure, produced by breathing against a resistance at the lips, is reflected backward into the respiratory passageway and has the physiological advantage of reducing expiratory bronchial constriction.

BIBLIOGRAPHY

- 1 MILLER, J. A., and RAPPAPORT, I. Relation of pulmonary function to fibrosis and emphysema, *ANN INT MED*, 1938, **xi**, 1644.
- 2 (a) JACKSON, C. L. Bronchoscopy and esophagoscopy, 1934, W. B. Saunders Co., Philadelphia.
- (b) MACKLIN, C. C. The dynamic bronchial trees, *Am Rev Tuberc*, 1932, **xxv**, 393.
- 3 (a) BARACH, A. L., MARTIN, J. D., and ECKMAN, M. Positive pressure in the treatment of pulmonary edema, *Jr Clin Invest*, 1936, **xv**, 466, *ibid*, *ANN INT MED* (to be published).
- (b) KERNAN, J. D., and BARACH, A. L. Role of helium in cases of obstructive lesions of trachea and larynx, *Arch Otolaryng*, 1937, **xxvi**, 419.
- 4 REICHERT, P. Oxygen utilization as an index of respiratory efficiency, *Jr Aviation Med*, 1936, **vii**, 63.
- 5 ECKMAN, M., and BARACH, A. L. Horizontal graphs by automatic intake of oxygen into basal metabolism machine, *Proc Soc Exper Biol and Med*, 1937, **xxxvi**, 138-141.
- 6 (a) BARACH, A. L. Use of helium as a new therapeutic gas, *Proc Soc Exper Biol and Med*, 1934, **xxxii**, 462.
- (b) BARACH, A. L. Use of helium as a therapeutic gas, *Anesth and Analg*, 1935, **xiv**, 210.
- (c) BARACH, A. L. Effects of the inhalation of helium mixed with oxygen on the mechanics of respiration, *Jr Clin Invest*, 1936, **xv**, 47.
- (d) BARACH, A. L. Use of helium in the treatment of asthma and obstructive lesions in the larynx and trachea, *ANN INT MED*, 1935, **ix**, 739.
- (e) BARACH, A. L. Rare cases not essential to life, *Science*, 1934, **lxix**, 593.
- (f) BARACH, A. L. The therapeutic use of helium, *Jr Am Med Assoc*, 1936, **cvii**, 1273.

- (g) MAYTUM, C K, PRICKMAN, L E, and BOOTHBY, W N Use of helium and oxygen in the treatment of severe intractable asthma, Proc Staff Meet, Mayo Clinic, 1935, *v*, 785
- (h) SCHWARTZ, A L The relief of status asthmaticus by helium, Jr Med, Cincinnati, Ohio, May 1938
- 7 VAN SLAKE, D D, and NEILL, J M Determination of volumes of gases in blood by vacuum extraction and manometric measurement, Jr Biol Chem, 1934, *lxiv*, 543
- 8 EVERSOLE, U H The use of helium in anesthesia, Jr Am Med Assoc, 1938, *cx*, 878
- 9 GRAESER, J B, and ROWE, A H Inhalation of epinephrine for relief of asthmatic symptoms, Jr Allergy, 1935, *vi*, 415, *ibid*, Inhalation of epinephrine hydrochloride for relief of asthma in children, Am Jr Dis Child, 1936, *lii*, 92
- 10 RICHARDS, D W, BARACH, A L, CROMWELL, H A, and DARLING, R C Inhalation of vaporized neo-synephrin in asthma and pulmonary emphysema (To be published)
- 11 (a) FITZHUGH, W M Neo-synephrine hydrochloride in otolaryngology, Arch Otolaryng, 1936, *xxiv*, 425
- (b) TAINTER, M L, and STOCKTON, A B Comparative actions of sympathomimetic compounds, Am Jr Med Sci, 1933, *clxxv*, 832
- 12 (a) TAINTER, M L Pharmacological actions of phenylethylamine, Jr Pharmacol and Exper Therap, 1929, *xxvi*, 29
- (b) JOHNSON, C A A study of neo-synephrin hydrochloride in the treatment of acute shock from trauma or hemorrhage, Surg, Gynec and Obst, 1936, *lxiii*, 35
- 13 MEAKINS, J C, and DAVIES, H W Respiratory function in disease, 1925, Oliver & Boyd, London
- 14 (a) KNIPPING, H W Dyspnoe, Beitr z Klin d Tuberk, 1933, *lxxvii*, 133
- (b) HERBST, R Die anatomischen und pathologisch-physiologischen Grundlagen des Asthma bronchiale, Immunitat Allergie u Infektionskr, 1933, *iv*, 3
- (c) STORM VAN LEEUWEN, W, VAN NIEKERK, J, and WELTZ, G A Studien über Atmung und Thoraxform bei Asthma und Emphysem, Munchen med Wchnschr, 1933, *lxxx*, 681
- (d) GAVAZZENI, M, and COTTI, L Der Einfluss der Stenosenatmung auf die Lungenventilation bei schwerer Arbeit, Beitr z Klin d Tuberk, 1934, *lxxxiv*, 433
- (e) HARRISON, T R, HARRISON, W G, JR, CALHOUN, J A, and MARSH, J P Congestive heart failure XVII Mechanism of dyspnea on exertion, Arch Int Med, 1932, *i*, 690
- (f) COURNAND, A, BROCK, H J, RAPPAPORT, I, and RICHARDS, D W Disturbance of action of respiratory muscles as a contributing cause of dyspnea, Arch Int Med, 1936, *lvi*, 1008-1026
- (g) CHRISTIE, R V The elastic properties of the emphysematous lung and their clinical significance, Jr Clin Invest, 1934, *xi*, 295
- (h) McCANN, W S, HURTADO, A, KALTREIDER, N L, and FRAY, W W Pulmonary function and respiratory function in the pulmonary fibroses, Trans Assoc Am Phys, 1934, *xli*, 81
- 15 (a) CAMPBELL, J M H, and POULTON, E P The effect on breathless subjects of residence in an oxygen chamber, Quart Jr Med, 1926, *xx*, 121
- (b) MEAKINS, J C, and CHRISTIE, R V The treatment of emphysema, Jr Am Med Assoc, 1934, *ciii*, 384
- (c) BARACH, A L, and RICHARDS, D W The effects of oxygen treatment in patients with pulmonary tuberculosis, Am Rev Tuberc, 1932, *xxvi*, 241
- (d) RICHARDS, D W, and BARACH, A L Effects of oxygen treatment over long periods of time in patients with pulmonary fibrosis, Am Rev Tuberc, 1932, *xxvi*, 253
- (e) RICHARDS, D W, and BARACH, A L Prolonged residence in high oxygen atmospheres Effects on normal individuals and on patients with chronic cardiac and pulmonary insufficiency, Quart Jr Med, 1934, *xxvii*, 437

- 16 BENEDICT, F G A helmet for use in clinical studies of gaseous metabolism, *New Eng Jr Med*, 1930, ccciii, 150
- 17 BARACH, A L, and RICHARDS, D W Effects of treatment with oxygen on cardiac failure, *Arch Int Med*, 1931, xlviii, 325
- 18 RICHARDS, D W To be published
- 19 LIVINGSTONE, J L Physical exercises for asthma published by the Asthma Research Council, Kings College, London, 1937
- 20 (a) HOFBAUER, L *Pathologische Physiologie der Atmung*, in BETHE, A, VON BERGMANN, G, EMBDEN, G, and ELLINGER, A *Handbuch der normalen und pathologischen Physiologie*, 1925, Julius Springer, Berlin, vol 2, p 337
 (b) SAENGER, M *Ueber Asthma und seine Behandlung*, 1910, S Karger, Berlin
 (c) Cournand, A, Brock, H J, RAPPAPORT, I, and RICHARDS, D W Disturbance of action of respiratory muscles as a contributing cause of dyspnea, *Arch Int Med*, 1936, lvi, 1008-1026
- 21 BARACH, A L Recent advances in inhalational therapy, *N Y State Jr Med*, 1937, xxxvii, 1
- 22 CAMPBELL, ARGYLL Face tent for oxygen administration, *Brit Med Jr*, 1936, 1245, *ibid*, *Lancet*, 1937, 82, *ibid*, *Modern Hospital*, 1937, xlviii, 90
- 23 BARACH, A L Pilot error and oxygen-want, *Jr Am Med Assoc*, 1937, cviii, 1868
- 24 PALMER, W W Personal communication
- 25 BARACH, A L The treatment of heart failure by continuous oxygen therapy, *Anesth and Analg*, 1935, xiv, 79-88

THE PRESSOR REACTION PRODUCED BY INHALATION OF CARBON DIOXIDE, STUDIES OF PATIENTS WITH NORMAL BLOOD PRESSURE AND WITH HYPERTENSION¹

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THE specific stimulating action of carbon dioxide on the vasomotor centers and its pressor effect on blood pressure have been known for some time. As early as 1864, Thiry¹ observed a rise of the blood pressure of animals during the inhalation of carbon dioxide and expressed the opinion that this was the result of stimulation of the vasomotor center, which produces a constriction of the peripheral arterioles. Traube² later confirmed this work and also looked on carbon dioxide as an excitant of the vasomotor center. In contrast to this work, Gaskell³ about the same time demonstrated by perfusion experiments that lactic acid dilated the arteries of the frog. Bayliss,⁴ in 1901, following Gaskell's work, demonstrated by perfusion fluid through the iliac arteries that both lactic acid and carbon dioxide produced an increase in the rate of flow of blood in the skinned limb of a frog. This was interpreted as a local effect of carbon dioxide on the blood vessels. Later, in 1918, Fleisch⁵ reported the results of perfusion experiments on the hind legs of frogs, he found that a low concentration (up to 3 per cent) of carbon dioxide caused arterial dilatation while stronger concentrations caused a constriction. He assumed that the dilator effect was attributable to the action on a nervous component and that the vasoconstriction was attributable to a direct action on the muscles of the arterioles.

In 1907, Henderson⁶ demonstrated that carbon dioxide was necessary to maintain normal vascular tone. This he accomplished by showing that in an etherized animal or man a loss of carbon dioxide produced by over-ventilation of the lungs caused a marked fall in blood pressure which was relieved by the administration of carbon dioxide. From that time to 1922 numerous workers confirmed the early work on the excitant properties of carbon dioxide on various nerve centers. In 1922, Dale and Evans⁷ presented evidence to show that the effect of inhalation of carbon dioxide was on the vasomotor centers in the bulb and the spinal cord. They maintained that the tonic action of the vasomotor centers was conditioned by the concentration of free carbon dioxide rather than "hydrogen ions" in the ar-

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[‡] Although Dr. Brown died in November 1935, the fact that he suggested this study and supervised it in its early stages seemed to the surviving authors to require that the paper be indexed under his name.

terial blood This may be attributable to the great power of carbon dioxide to penetrate all membranes

Porter⁸ during the war used a 3 per cent concentration of carbon dioxide to increase the blood pressure of soldiers who were in a state of shock In 1922, Schneider and Truesdell⁹ demonstrated that inhalation of 1 to 8 per cent carbon dioxide by normal individuals was followed by an increase in the pulse rate, an increase in the systolic and diastolic blood pressure and an increase in the pulse pressure, particularly after the concentration of carbon dioxide had reached 3 per cent

Raab,^{10, 11} in 1929, reported that during the inhalation of carbon dioxide the increase in the blood pressure of patients who had essential hypertension was several times as great as that noted in a group of normal persons He attributed these increases in blood pressure to an increased sensitivity of the vasomotor centers to changes in carbon dioxide tension Many investigators have been concerned with the question as to whether essential hypertension is central or peripheral in origin Ellis and Weiss,¹² in 1930, showed that the increased blood pressure in cases of hypertension is the result of a contraction of the peripheral vascular system and that it is not the result of primary changes in the general blood volume, cardiac output, circulation through the lungs, or velocity of the blood flow Investigators have assumed that diminishing the supply of blood and oxygen to vasomotor centers was the most essential condition for increased activity of these centers Another assumption is that the accumulation of acid substances, particularly lactic acid, which results from a lack of oxygen, is a factor in increasing activity or tonus of the vasomotor centers This forms the basis of the most recent hypothesis of essential hypertension In 1931, Raab^{13, 14} attempted to produce essential hypertension in animals in an effort to determine its pathogenesis He produced hypertension by irritation of the vasomotor centers by decreasing the supply of oxygen or by a perfusion of the hypothetical vasomotor centers with lactic acid When inhalation of carbon dioxide was added to either or both of these conditions a considerably greater rise in blood pressure occurred This increased sensitivity also could be produced by purely nervous stimuli from the periphery Raab concluded that essential hypertension could be considered the result of local deficiency of oxygen and the accumulation of lactic acid within the vasomotor centers of the brain stem as a consequence of disturbances in the local circulation, such as spasm or sclerosis The actual blood pressure in hypertension would accordingly be determined by the sum of the stimuli resulting from oxygen deficiency and accumulation of lactic acid and also by the abnormally increased responses of blood pressure to the stimulus of the normal carbon dioxide tension of the blood and different kinds of sensory and emotional stimuli

The more recent conception of the fundamental abnormality in cases of essential hypertension is that the central vasomotor mechanism is hypersensitive and reacts excessively to many forms of stimulation, such as

those which are sensory, thermal, and emotional. Changes in circulation of the brain which result from organic arterial disease or spasm do not appear to play a rôle in elevation of blood pressure in cases of hypertension except in the later stages. Studies which have been made on the constitutional nature of essential hypertension by employing a standard stimulus^{15, 16} (cold), which effects a sharp, thermosensory vasopressor reflex, are important. The hyperreactive vasopressor response to cold is present during the early life of most children of hypertensive parents. It would be difficult to assume that organic or circulatory factors exist in the brain of persons who eventually will have hypertension.

The present study was carried out to determine whether the pressor reactions of normal and hypertensive persons were qualitatively or quantitatively different following the inhalation of carbon dioxide, and to compare these responses with those which occur as a result of the cold test.

MATERIAL

The tests were carried out on 65 patients, 24 of these patients had a normal blood pressure and 41 had varying degrees of hypertension. All were ambulatory patients and none had evidence of cardiac or renal insufficiency. The ages of the patients varied from 20 to 60 years, 36 were men and 29 were women. For the observations the patients were divided into two groups depending on the method of study employed.

Group 1 was composed of 45 patients. This group was further subdivided into three groups. Group A was composed of 15 patients whose blood pressure was normal. Group B was composed of 21 patients who had essential hypertension without demonstrable organic change in the arterioles of the retinae except as shown in the table which deals with this group. Group C was composed of nine patients who had essential hypertension which was associated with definite organic changes in the arteries of the retinae.

Group 2 consisted of 20 patients, 9 had a normal blood pressure and 11 had varying degrees of hypertension. The distribution according to age and sex was similar to that in group 1.

METHODS

Cold Test In performing the cold test the patient is placed in a recumbent position for 30 minutes, or until the blood pressure has attained the basal level. The cuff is placed on one arm of the patient and the hand on the opposite side is placed in ice water at 4° C well above the wrist for one minute. The value for the blood pressure is determined at least three times while the hand is in the ice water. The highest value for the systolic and diastolic pressure is recorded as the measure of response. The hand is then removed from the ice water.

Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen Before the inhalation of carbon dioxide the patient is placed in a recumbent

position for 20 minutes until the basal blood pressure and basal pulse rate are established. The mask which is used to insure proper inspiration of the carbon dioxide is put on the patient and allowed to remain until he becomes accustomed to breathing with it on and until the blood pressure and pulse rate return to approximately basal levels. The mask is then attached to a tank which contains a mixture of 10 per cent carbon dioxide and 90 per cent oxygen, this mixture is administered for five minutes. The blood pressure and pulse rate are recorded every minute. The number of respirations are noted. No ill effects were noted from the inhalation of the carbon dioxide, whatever minor distress (slight dyspnea, light headedness, and so forth) was present quickly disappeared when the inhalation of carbon dioxide was discontinued. The number of respirations was slightly increased (an average of eight) while the depth was definitely increased. The pulse rate increased while the patients breathed carbon dioxide. This is discussed more fully in the consideration of the various groups.

The difference between the studies in group 1 and group 2 was that in group 1, in addition to the preliminary cold test another similar test was performed during the inhalation of carbon dioxide. In group 2 the second cold test was performed five minutes after the removal of the mask, when the blood pressure had returned to the previous basal levels.

DATA OBTAINED FROM STUDY OF PATIENTS IN GROUP 1

Cold Test The results obtained in group A are shown in tables 1 and 2. The average increase in blood pressure from the basal level in this group during the application of the cold test was 13.4 mm. of mercury for the systolic pressure and 11 mm. for the diastolic pressure. In group B (tables 2 and 3) the average increase in blood pressure from the basal level was 28.9 mm. of mercury for the systolic pressure and 19.1 mm. for the diastolic pressure. In group C the average increase in blood pressure from the basal level was 32.4 mm. of mercury for the systolic pressure and 24.5 mm. for the diastolic pressure.

The Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen In group A the inhalation of 10 per cent carbon dioxide caused an average increase in the blood pressure from the average basal level, of 25.2 mm. of mercury for the systolic pressure and 14.6 mm. for the diastolic pressure (tables 1 and 2). In four cases in which the blood pressure was normal, no increase occurred or the increase was less than that produced by the cold test alone. The pulse rate increased an average of eleven beats for each minute that the carbon dioxide and oxygen were inhaled. In six cases the increase was negligible, while in the three cases in which there was the greatest increase in systolic blood pressure during the inhalation of carbon dioxide and oxygen, the increase in the pulse rate was the greatest (20 to 40 beats per minute). In Group B the inhalation of carbon dioxide and oxygen caused an average increase of 33.7 mm. of mercury in the systolic

TABLE I

Effects of Cold and Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen on the Blood Pressure in Group A

Case	Age, years, and sex	Systolic and diastolic blood pressure, mm of mercury			
		Basal values	During application of cold	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen and application of cold
1	42 M	115/73	128/75	120/90	138/100
2	24 F	114/80	122/94	136/103	140/110
3	48 F	120/75	128/85	120/80	140/90
4	35 M	110/80	120/85	120/90	140/100
5	36 M	112/75	120/85	130/80	130/80
6	20 M	110/75	125/85	130/80	130/90
7	43 M	118/74	128/86	150/85	160/90
8	28 M	110/80	125/80	160/100	160/100
9	27 M	110/70	120/80	160/100	160/100
10	27 F	110/78	130/90	130/80	130/82
11	29 F	86/60	104/80	130/80	130/80
12	37 M	88/68	98/70	105/70	110/70
13	29 F	90/65	115/90	124/94	130/95
14	49 M	75/50	87/68	110/80	110/75
15	26 M	108/65	128/80	130/75	140/85
Mean values	Systolic pressure	105.1 \pm 2.3	118.5 \pm 2.3	130.3 \pm 2.8	136.5 \pm 2.7
	Diastolic pressure	71.2 \pm 1.5	82.2 \pm 1.3	85.8 \pm 1.7	89.8 \pm 1.9

TABLE II

Effects of Cold, Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen, and the Application of Cold during the Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen in Group 1

Group	Cases	Systolic and diastolic blood pressure, mm of mercury			
		Average basal values	Average increase during		
			Cold test	Inhalation of 10 per cent carbon dioxide and 90 per cent oxygen	Inhalation of 10 per cent carbon dioxide and 90 per cent oxygen and application of cold
A (blood pressure normal)	15	105.1/71.2	13.4/11.0	25.2/14.6	31.4/18.6
B (hypertension without organic changes in retinal arteries)	21	134.3/87.8	28.9/19.1	33.7/20.1	48.5/28.1
C (hypertension with changes in retinal arteries)	9	156.3/105.1	32.4/24.5	23.4/15.7	35.7/25.8
B and C (hypertension)	30	140.9/93.0	30.0/20.7	30.6/18.8	44.6/27.4

pressure and 20.1 mm in the diastolic pressure. In 11 cases no increase in blood pressure occurred or the increase was less than that produced by

TABLE III

Effects of Cold and Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen on the Blood Pressure in Group B

Case	Age, years, and sex	Changes in ocular fundi	Systolic and diastolic blood pressure, mm of mercury				
			Basal values	During application of cold	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen and application of cold	
1	34 M	0	140/98	150/100	150/100	155/105	
2	42 F	0	140/100	162/108	130/90	154/100	
3	25 M	0	130/86	152/100	152/92	165/110	
4	47 F	0	120/76	160/100	155/100	175/110	
5	23 M	0	132/90	154/110	165/115	172/117	
6	47 M	0	140/108	180/140	158/120	180/140	
7	45 M	Arterioles narrowed	125/100	145/115	125/100	155/110	
8	49 M	Arterioles narrowed	120/80	140/100	160/110	160/112	
9	22 M	Arterioles narrowed	140/78	158/105	165/100	175/100	
10	43 F	Arterioles narrowed	135/95	165/120	180/120	200/130	
11	27 M	Arterioles narrowed	152/82	180/100	190/118	210/120	
12	49 F	Arterioles narrowed	150/80	170/90	195/110	210/115	
13	41 F	Arterioles narrowed	150/100	180/120	210/130	210/130	
14	43 M	Arterioles narrowed	150/90	230/148	220/120	240/160	
15	38 M	Arterioles narrowed	150/98	190/110	190/115	205/120	
16	60 M	Arterioles narrowed	130/58	164/80	190/100	200/100	
17	26 F	Arterioles narrowed	132/100	165/100	200/130	208/140	
18	36 M	Arterioles narrowed	140/80	152/100	170/100	190/110	
19	26 F	Arterioles narrowed	105/70	150/109	145/95	162/100	
20	21 M	Arterioles narrowed	130/90	142/90	140/108	152/105	
21	31 M	Arterioles narrowed	110/85	140/100	138/92	160/100	
Mean values			Systolic pressure	134.3 ± 2.0	163.2 ± 3.2	168.0 ± 4.0	182.8 ± 3.7
			Diastolic pressure	87.8 ± 1.8	106.9 ± 2.3	107.9 ± 1.7	115.9 ± 2.4

the cold test alone. In group B the average increase in pulse rate during the inhalation of carbon dioxide and oxygen was 17 beats per minute. There was no apparent correlation between the increase in pulse rate and the in-

crease in blood pressure In group C (tables 2 and 4) the average increase in the blood pressure during the inhalation of carbon dioxide and oxygen was 23.4 mm of mercury for the systolic pressure and 15.7 mm for the diastolic pressure This was less than the average increase produced by the cold test alone for this group The average increase in pulse rate was 11 beats per minute

The Application of the Cold Test during the Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen In group A (tables 1 and 2),

TABLE IV

Effects of Cold and Inhalation of 10 Per Cent Carbon Dioxide and 90 Per Cent Oxygen on the Blood Pressure in Group C

Case	Age, years, and sex	Changes in ocular fundi	Systolic and diastolic blood pressure, mm of mercury			
			Basal values	During application of cold	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen	During inhalation of 10 per cent carbon dioxide and 90 per cent oxygen and application of cold
1	43 F	Sclerosis, grade 1	120/80	150/110	152/106	156/120
2	33 F	Sclerosis, grade 1	140/95	158/110	154/112	172/120
3	40 F	Sclerosis, grade 1	152/110	180/130	175/120	200/150
4	32 F	Sclerosis, grade 1	135/100	170/120	170/125	180/130
5	33 F	Sclerosis, grade 1	180/130	235/160	190/140	180/130
6	48 F	Sclerosis, grade 1	140/96	180/112	182/120	200/125
7	57 M	Sclerosis, grade 3, and hemorrhages	190/125	220/175	210/135	230/155
8	51 M	Sclerosis, grade 3	140/100	150/110	140/100	150/110
9	44 F	Arterioles narrowed	210/110	255/140	245/130	260/138
Mean values			156.3 ± 6.8	188.7 ± 8.63	179.7 ± 7.4	192.0 ± 7.9
			105.1 ± 3.5	129.6 ± 5.5	120.8 ± 3.2	130.9 ± 3.3

when a cold test was performed during the inhalation of 10 per cent carbon dioxide and 90 per cent oxygen, the average increase was 31.4 mm of mercury for the systolic pressure and 18.6 mm for the diastolic pressure These increases were greater than those which were produced by either the cold test alone or the inhalation of carbon dioxide and oxygen However, in seven cases in this group the increase in blood pressure produced by the application of the cold test during the inhalation of carbon dioxide and oxygen was no greater than the increase produced by the inhalation

of carbon dioxide In group B (tables 2 and 3) the application of cold during the inhalation of carbon dioxide and oxygen produced an average increase of 48.5 mm of mercury in the systolic pressure and an average increase of 28.1 mm in the diastolic pressure These were the greatest increases noted in group 1 The increase in the systolic pressure was three and six-tenths greater and the increase in the diastolic pressure was two and a half times greater than were the increases which occurred in the systolic and diastolic pressures respectively when normal persons were subjected to the cold test The increase in the systolic and diastolic pressure was one and nine-tenths greater than that which was obtained when normal persons were inhaling carbon dioxide and oxygen The increase in the systolic pressure was one and six-tenths greater and the increase in the diastolic pressure was two and four-tenths greater than were the increases which were obtained in these respective pressures when the cold test was applied to normal persons who were inhaling carbon dioxide and oxygen In group C (tables 2 and 4) the application of cold during the inhalation of carbon dioxide and oxygen produced an average increase of 35.7 mm of mercury in the systolic pressure and an average increase of 25.8 mm in the diastolic pressure These increases were not as great as the respective increases which were obtained in the group of patients who had pre-organic hypertension (group B), but in group C the average value for the systolic pressure was 22 mm of mercury higher and that for the diastolic pressure was 17.3 mm higher than were the respective values in group B In all but one of the cases in group C the increases in the systolic and diastolic blood pressure which were produced when the cold test was applied during the inhalation of carbon dioxide and oxygen were greater than the increases which were produced by the inhalation of carbon dioxide and oxygen

When the patients who had hypertension (groups B and C) were considered as a single group it was found that the increases in blood pressure which were produced by the application of cold, by the inhalation of carbon dioxide and oxygen and by the application of cold during the inhalation of carbon dioxide and oxygen were nearly twice as great as were the increases which were produced in cases in which the blood pressure was normal (group A) However, this same quantitative difference was produced by the cold test alone at a lower level of blood pressure

DATA OBTAINED FROM STUDY OF PATIENTS IN GROUP 2

Group 2 included 9 persons whose blood pressure was normal and 20 patients who had varying degrees of hypertension In the study of this group the cold test was not performed during the inhalation of carbon dioxide and oxygen but was performed five minutes after the inhalation had been discontinued and the blood pressure had returned to the previous basal levels This was done in order to determine whether the vasomotor centers would be more sensitive to the application of cold following the inhalation of carbon dioxide and oxygen than they were before or during the inhala-

tion In the nine cases in which the blood pressure was normal the application of cold produced an average increase of 15 mm of mercury in the systolic pressure and an average increase of 13 mm in the diastolic pressure During the inhalation of 10 per cent carbon dioxide and 90 per cent oxygen, the average increase in the systolic pressure was 39 mm of mercury and the average increase in the diastolic pressure was 21.8 mm The application of cold five minutes after the inhalation of carbon dioxide and oxygen had been discontinued produced an average increase of 17.7 mm of mercury in the systolic pressure and an average increase of 16.6 mm in the diastolic pressure These increases were similar to those which were produced by the application of cold before the inhalation of carbon dioxide and oxygen The average increase in the pulse rate during the inhalation of carbon dioxide and oxygen was 20 beats per minute This was slightly greater than the increase noted in group 1

In the eleven cases in which the patients had varying degrees of hypertension the application of cold produced an average increase of 37.4 mm of mercury in the systolic pressure and an average increase of 25.7 mm in the diastolic pressure The inhalation of carbon dioxide and oxygen produced an average increase of 54.8 mm of mercury in the systolic pressure and an average increase of 32.4 mm in the diastolic pressure Five minutes after the inhalation of carbon dioxide and oxygen had been discontinued the application of cold produced an average increase of 30.3 mm of mercury in the systolic pressure and an average increase of 28.8 mm in the diastolic pressure In a very few cases the increases which were observed when cold was applied five minutes after the inhalation of carbon dioxide and oxygen had been discontinued were slightly greater than the increases which were observed when cold was applied before the inhalation In cases in which cold was applied one or two minutes after the inhalation of carbon dioxide and oxygen had been discontinued the increases were greater than those observed when cold was applied before the inhalation, but this response disappeared five minutes after the inhalation had been discontinued The effect of carbon dioxide on the vasomotor center apparently disappears in about five minutes

COMMENT

The inhalation of 10 per cent carbon dioxide and 90 per cent oxygen produced an increase in the blood pressure of normal and hypertensive persons There was no qualitative difference in the vasopressor response of normal and hypertensive persons but a significant quantitative pressor reaction was obtained when cold was applied during the inhalation of the carbon dioxide and oxygen When groups B and C were considered as a single group we found that the average increases produced in the blood pressure by the application of cold were the same as those produced by the inhalation of carbon dioxide and oxygen When the cases of hypertension were divided into those in which the hypertension was in the early or pre-organic stage and those in which the hypertension was in the advanced stage it was found

that the increases which were produced in the blood pressure by the application of cold were greater in cases of early or pre-organic hypertension than they were in cases of advanced hypertension. This was particularly true when cold was applied during the inhalation of carbon dioxide and oxygen. The basal blood pressure was lower in cases of pre-organic hypertension than it was in cases of advanced hypertension. If the actual height or "ceiling" of the blood pressure is used as a criterion, the blood pressure was higher in cases of advanced hypertension. The average increases in the blood pressures of normal and hypertensive persons were greater when cold was applied during the inhalation of carbon dioxide and oxygen than they were when cold was not applied during the inhalation. This confirms the experimental work of Raab. This effect may be said to be the result of the combined action of several stimuli. The recent work of Bolton, Carmichael and Williams¹⁷ did not reveal that alteration in the tension of gas in the blood affected the peripheral vessels. The vascular responses produced by the inhalation of carbon dioxide and oxygen are dependent on the integrity of the sympathetic nervous system and are under the control of the central nervous system. Since carbon dioxide has a specific stimulating effect on the vasomotor centers, the definite increase in blood pressure which occurs during the inhalation of carbon dioxide and oxygen may be assumed to indicate some hypersensitivity of the vasomotor centers. When cold was applied during the inhalation of carbon dioxide and oxygen a further increase took place. This might have been caused by a reflex transmission of peripheral stimulation to a higher reactive central mechanism that was still further sensitized by the increased concentration of carbon dioxide in the blood, but the response was most likely the result of several stimuli.

These observations are important in attempting to explain the disturbed mechanism in essential hypertension. They demonstrate that a stimulus applied to the periphery (local application of cold), or applied centrally by increasing the carbon dioxide concentration in the blood, increased the blood pressure of normal and hypertensive persons. They throw no light on the question as to why the hypertensive person responds to a greater extent than does the normal person. Whatever the fundamental fault is, it does not occur in adult life with the onset of high blood pressure, but occurs years before there is an increase in the blood pressure. This fault concerns the constitutional nature of the behavior of the autonomic nervous centers and may be influenced by hereditary factors. Similar physiologic faults will probably be found in other centers which regulate autonomic nervous activity. It is futile to make hypotheses in the present state of our knowledge. The entire question of differences in psychic behavior, in personality, and in the reaction of the central nervous system to its environment is intimately concerned in this problem.

SUMMARY

The results which we obtained with the cold test alone were comparable to those obtained by Hines and Brown on normal and hypertensive persons.

The inhalation of 10 per cent carbon dioxide and 90 per cent oxygen produced an increase in the blood pressure of both normal and hypertensive persons. The increase in blood pressure was greater and the ultimate height reached was greater in cases of hypertension than it was in cases in which the blood pressure was normal. The studies did not produce any evidence as to why the hypertensive person responds to a greater degree than does a normal person.

The increase in blood pressure produced by the application of cold during inhalation of carbon dioxide and oxygen might be interpreted as the result of a reflex transmission of peripheral stimulation to a higher reactive central mechanism that was still further sensitized by the increased concentration of carbon dioxide in the blood, but the response most likely is the combined result of several stimuli.

REFERENCES

- 1 THIRY, L. Ueber das Verhalten der Gefassnerven bei Storungen der Respiration, *Centralbl f d med Wissensch*, 1864, ii, 722
- 2 TRAUBE, L. Ueber periodische Thatigkeits—Ausserungen des vasomotorischen- und hemmungs- Nervencentrums, *Centralbl f d med Wissensch*, 1865, ii, 881-885
- 3 GASKELL, W H. The involuntary nervous system, 1916, Longmans, Green and Company, London, 178 pp
- 4 BAYLISS, W M. The action of carbon dioxide on blood vessels, *Jr Physiol*, 1901, xxvi, xxvii-xxviii
- 5 FLEISCH, ALFRED. Experimentelle Untersuchungen uber die Kohlensaurewirkung auf die Blutgefasse, *Pfluger's Arch*, 1918, clxxi, 86-133
- 6 HENDERSON, YANDELL. Apapnia and shock. I. Carbon-dioxide as a factor in the regulation of the heart-rate, *Am Jr Physiol*, 1908, xxi, 126-156
- 7 DALE, H H, and EVANS, C L. Effects on the circulation of changes in the carbon-dioxide content of the blood, *Jr Physiol*, 1922, lvi, 125-145
- 8 PORTER, W T. Shock from fat embolism of the vasomotor center, *Am Jr Physiol*, 1924-1925, lxxi, 277-315
- 9 SCHNEIDER, E C, and TRUESDELL, D. The effects on the circulation and respiration of an increase in the carbon dioxide content of the blood in man, *Am Jr Physiol*, 1922, lxxiii, 155-175
- 10 RAAB, W. Die Beziehungen zwischen CO₂-Spannung und Blutdruck bei Normalen und Hypertonikern. Beitrag zur Pathogenese der nicht "nephritischen" Hypertonien, *Ztschr f d ges exper Med*, 1929, lxxviii, 337-370
- 11 RAAB, W. Zur Pathogenese der essentiellen Hypertonie, *Klin Wchnschr*, 1929, viii, 1130
- 12 ELLIS, L B, and WEISS, SOMA. The local and systemic effects of arterio-venous fistula on the circulation in man, *Am Heart Jr*, 1930, v, 635-647
- 13 RAAB, W. Funktionsprufung des zentralen Vasomotorenapparates in verschiedenen Lebensaltern, *Ztschr f klin Med*, 1931, cxviii, 618-629
- 14 RAAB, W. Central vasomotor irritability. Contribution to the problem of essential hypertension, *Arch Int Med*, 1931, xlvii, 727-757
- 15 HINES, E A, JR, and BROWN, G E. A standard stimulus for measuring vasomotor reactions: its application in the study of hypertension, *Proc Staff Meet Mayo Clinic*, 1932, vii, 332-335
- 16 BROWN, G E. Functional or preclinical stage of essential hypertension, *Jr Tennessee State Med Assoc*, 1933, xxvi, 321-325
- 17 BOLTON, B, CARMICHAEL, E A, and WILLIAMS, D J. Mechanism of peripheral vascular responses to changes in blood gas tension in man, *Jr Physiol*, 1936, lxxxviii, 113-126

CONSTITUTIONAL REACTIONS FROM BACTERIAL VACCINES^{*}

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ALTHOUGH much has been written about local and focal reactions, little or no attention has been paid to constitutional reactions from bacterial vaccine injections. These systemic bacterial reactions are entirely different from the constitutional reactions sometimes encountered following treatments with food, animal epidermal, pollen, or other kinds of protein extracts. An overdose of vaccine will frequently cause an aggravation of the patient's trouble, but the type of constitutional reaction that I am about to describe is a definite shock reaction, comparable to that produced by the intentional intravenous injection of a small dose of typhoid vaccine in foreign protein therapy.

In allergic individuals, constitutional reactions from food, animal epidermal, pollen, or other nonbacterial protein extracts, almost always occur inside of 30 minutes following the injection, and manifest themselves as itching of the palms of the hands, or irritation of the nose and throat, or as a definite attack of urticaria, hay-fever, or asthma. Whenever any of the dose is accidentally injected into a blood vessel, the constitutional reaction takes place almost instantaneously.

The bacterial type of constitutional reaction manifests itself within one-half hour to several hours following the vaccine injection. It always starts with a chill, which may vary from mere chilly sensations to a definite, shaking chill. Nausea and vomiting occasionally occur at this stage, particularly in children. The chill is soon succeeded by fever ranging anywhere from 100° to 105°. There is malaise, and usually aches and pains throughout the body. The reaction simulates quite closely, therefore, the early stages of an attack of grippe or influenza. After a few hours, however, the temperature usually returns to normal, and by the next day the patient has either fully recovered, or is left with only a feeling of weakness which soon passes off. Occasionally, the fever persists until the following day. Although such a reaction is not necessarily dangerous, it is decidedly unpleasant, and may cause a nervous patient to become apprehensive about subsequent vaccine treatment.

This type of constitutional reaction which occasionally occurs in bacterial vaccine therapy, is never encountered in treatment with food, animal epidermal, pollen, or other kinds of protein extracts. It can happen with both stock and autogenous vaccines, and in nonallergic as well as allergic individuals. Although a constitutional reaction is more likely to occur following the larger doses of a strong vaccine, it is not dependent upon the size of the dose for its production, as it can follow a repeated dose of the

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same vaccine, where the preceding dose had failed to produce any unpleasant symptoms

This distinctive type of constitutional reaction is evidently due to accidental injection of some or all of the vaccine dose into a blood vessel, as the symptoms can be duplicated by an intentional intravenous injection of bacterial vaccine. A subcutaneous injection of a dose of potent vaccine is almost always followed by a local reaction which can be both seen and felt, reaching its height in about 24 hours. When a vaccine treatment is followed by a constitutional reaction, however, there is almost invariably a negligible local reaction, or even none at all, indicating that some or all of the dose has been abruptly carried away from the site of injection.

The way to prevent these bacterial protein shock reactions is to keep the vaccine from directly entering the blood stream, by means of the following precautions. Because of its lack of vascularity, the outer part of the upper arm, about midway between shoulder and elbow, is the best site for vaccine injections. After the hypodermic needle has been inserted subcutaneously, but before any of the vaccine is injected, the piston of the syringe should be sharply retracted to see if any blood comes back into the syringe. If blood appears, the needle should be withdrawn and inserted in another spot, and the piston retraction repeated, before the dose of vaccine is actually injected. The vaccine should be injected slowly, and with the larger doses, the syringe piston should be retracted several times during the course of the injection to make sure that the tip of the needle has not slipped into a small blood vessel. After all of the dose is injected, a small pledget of sterile cotton, moistened with alcohol, should be pressed over the site of injection and held there while the needle is being withdrawn and for a short time thereafter, to prevent any of the vaccine from tracking back through the needle wound into a superficial vessel that may have been punctured by the passage of the needle through the tissues. I consider this last precaution to be quite important in the prevention of constitutional reactions. The injection site should never be massaged. By careful observance of the above-mentioned technic it is possible, except on rare occasions, to prevent the vaccine from immediately entering the blood stream.

Treatment of these shock reactions when they do occur, consists of the oral administration of ephedrine and amytal (iso-amyl ethyl barbituric acid), or ephedrine with phenobarbital, and rest in bed during the brief febrile stage.

SKIN TESTING FOR BRUCELLOSIS (UNDULANT FEVER) IN SCHOOL CHILDREN¹

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IN human beings cutaneous hypersensitivity to organisms of the genus *Brucella* was first investigated by Fleischner and Meyer¹ in 1918. Using a saline suspension of organisms they tested 75 infants who had been fed milk containing *B. abortus* and found two with a specific skin sensitivity. Burnet,² subsequently, used a broth filtrate and demonstrated a relationship between skin reactivity and the presence of specific agglutinins in the blood stream. Since then the test has been used frequently for the diagnosis of undulant fever^{3, 4, 5, 6, 7, 8, 9, 10, 11} also in surveys designed to evaluate the incidence of infection in various occupational groups, such as meat packers, veterinarians and laboratory workers^{12, 13, 14, 15, 16}. The variety of antigens which have been used precludes specific comparison of the results of investigators, though they have usually agreed that a positive skin test indicates some past contact with the organism. The high percentage of positive reactors in those groups closely associated with animal carcasses and persons with long periods of association with domestic animals points strongly to animal contact as an important factor in the development of the positive reaction.

Certain observations have made the interpretation of the skin test difficult. For instance, some individuals from whose blood *B. abortus* has been cultivated have been shown to have negative skin reactions^{19, 20, 21, 22, 23, 24}. Moreover, it is common experience that many individuals develop hypersensitivity to the antigen without having been aware of symptoms or signs of the disease. Furthermore, for years after recovery from the disease skin reactivity is usually retained. Therefore, the skin test may seem of little value in the diagnosis of the individual case, but further knowledge of the epidemiology and incidence of brucellosis in man may be gained by its use on large groups. The following report presents data secured on children of school age in Kansas City, Kansas, in the course of one of three surveys conducted by the National Institute of Health to study the incidence of chronic brucellosis.

Kansas City, Kansas, has an urban population of 126,000 divided into five districts which grew up independently and are separated by such boundaries as ravines, rivers and transportation systems. The incidence of Bang's disease among dairy herds supplying milk to this community as

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We wish to express our appreciation for the hearty cooperation of the Kansas State Board of Health, Dr. Clifton Hall, and Dr. Alice Evans of the National Institute of Health.

determined by agglutination tests performed during the last ten years has varied from 12 to 27 per cent. Rapid method agglutination tests which have been made in local private and hospital laboratories during the past two years revealed that 5 per cent of 5000 sera tested were positive in dilutions of 1:10 or higher.

Not only the factor of milk consumption but that of age should be considered in a group of school children. It has long been assumed that the greater percentage of positive skin reactors to various bacterial antigens in older age groups was explicable on the basis of prolonged exposure and subclinical infections. That these are the sole factors involved has been questioned, several investigators having suggested that age *per se* may be a factor in determining skin reactivity. Various investigations which have supported this view have been reviewed by Baumgartner¹⁷. It is now accepted that the skin of the very young infant does not react like that of the older subjects regardless of the immune state involved. This difference may be of no importance in the present study, but it does seem of some interest to point out that infections due to brucellae in children have been infrequently reported in the literature although the greater exposure through milk ingestion would obviously be in younger age groups.

METHODS

The antigen used for intradermal tests was Huddleson's¹⁸ "brucellergin," a fat-free nucleoprotein derivative, kindly supplied by him. For the tests 0.1 c.c. of a 1:10,000 dilution was used. Readings were made in 48 hours. Tests were considered positive only if erythema and edema measuring at least 5 by 5 mm. were present.

The school children were given routine tuberculin tests¹ (0.0005 mg. P.P.D.) on the opposite arm at the same time the brucellergin skin tests were performed.

In the control experiments, comparing the results of tests made with brucellergin and heat-killed vaccine, 0.04 c.c. of the latter was used for each test, both tests being made simultaneously, one on each forearm. Readings were made after 48 hours and after 7 days. The vaccine used was standardized to a nephelometer number 3 which represents approximately 6 billion organisms per c.c.

RESULTS

1 *Comparison of Brucellergin and Heat-Killed Vaccine in Skin Tests*
One group of 168 persons was tested simultaneously with both vaccine and brucellergin. The results are summarized in table 1. The subjects were all inmates of a county farm, public charges, some of whom had been moved from other institutions, many of whom had lived for years under some kind of institutional regime. Positive reactors had been found in the

* These tuberculin tests were performed by Dr. Clifton Hall of the Kansas State Department of Health.

herds supplying one of the institutions, in which these subjects had been housed—though satisfactory data concerning the incidence of herd infections were lacking. Readings were recorded as follows

- no reaction or one measuring less than 5 by 5 mm at 48 hours and no reaction in 8 days
- + reaction measuring 5 by 5 mm or over but less than 10 by 10 mm at 48 hours and little or no reaction at 8 days
- ++ reaction of 10 by 20 mm at 48 hours, persistent reaction at 8 days with slight pigmentation
- +++ more than 20 by 20 mm erythema and edema at 48 hours with persistent reaction at 8 days
- ++++ more than 30 by 30 mm reaction at 48 hours and ulceration at 8 days

TABLE I

Comparison of Results in Intradermal Tests with Brucellergin and Vaccine in 163 Persons

Type of Antigen	Number of Persons Exhibiting Reactions					
	—	+	++	+++	++++	Total
Brucellergin	119	21	12	11	0	163
Vaccine	74	42	27	11	9	163

The severity of the reactions with the two antigens differed, though in the same person the same relative degree of severity was found, i.e., the person with a ++++ reaction to vaccine had a +++ reaction to brucellergin, the most severe reaction found with this antigen. The ++++ reactions were those with ulceration and found only when vaccine was used. Brucellergin detected these very sensitive individuals but gave rise to less severe reactions.

Blood was taken from 14 of the more severe reactors seven days after skin testing and the sera tested for specific agglutinins and opsonocytaphagic activity, using the technics described by Evans²⁰. In all but one individual specific agglutinins were demonstrated in dilutions varying from 1:10 to 1:320. Two months later 13 of these subjects were retested. All gave positive agglutinin reactions, 11 of the 13 with higher titers—two as high as 1:1280. This sharp rise in agglutinin titer was attributed to the antigenic properties of the material used for skin tests, because the subjects showed little evidence of concomitant disease. They were, however, old people with many complaints and reliable histories and clinical studies were not available. The marked increase in the agglutinin titer (1:10 to 1:1280 for example) from seven days to two months after the initial skin test indicates that the results of agglutination tests should be regarded with suspicion if the individual has previously been skin tested. Opsonocytaphagic

activity varied so much in the two months interval between testings that no significant statement concerning the influence of skin testing on this phenomenon can be made

2 *The Relationship of Skin Sensitivity to Age* Table 2 summarizes the results of brucellergin skin tests on 7,122 school children

TABLE II

Relationship of Age to the Result of Intradermal Brucellergin Tests in 7,122 Children

Age	Male		Female		Total		
	Tested	Positive	Tested	Positive	Tested	Positive	Per cent Positive
4-9	629	32	584	37	1213	69	5.7
10-14	1671	172	1729	160	3400	332	9.7
15-19	1353	152	1156	89	2509	241	9.6
Total	3653	356	3469	286	7122	642	9.0

Nine per cent of the entire group gave positive reactions. The children less than 10 years of age showed a significantly lower percentage of positive reactions (5.7). In the two older age groups (10-14 and 15-19) about the same percentages of positive reactions were found (9.6). The only difference between the sexes was found in the 15-19 year group of white children, with 11.2 per cent of males and 7.7 per cent of females showing positive skin tests. This difference was not found in colored children of this age.

3 *Analysis of Results by Schools* In table 3 a comparison of the results in the different schools shows a range in percentage of positive reactors from 2.7 to 18.1.

TABLE III

Comparison by Schools

	Number Tested	Number Positive	Per cent Positive
Junior and Senior High A	711	129	18.1
Junior and Senior High B	1181	146	12.36
Junior and Senior High C	1135	107	9.42
Junior and Senior High D (Colored)	1117	31	2.7
Grade Schools A	2776	203	7.3
Unclassified	202	26	12.8

The highest percentage was found in the junior and senior high schools located in the southwestern section of the city. Here, the population is relatively less dense and many families keep milk cows, goats, hogs and chickens. Many of these people drink raw milk not controlled by city regulations and also they may have direct contact with infected animals.

A survey showed that at least two-thirds of all families keeping animals in the city live in this section. On the other hand, in the northeastern section of the city where the population is almost entirely colored and virtually no domestic animals are kept, only 2.7 per cent of students in the junior and senior high schools showed positive skin reactions. The milk consumed in this area is bought from dairies or grocery stores where the supply is regulated by the city milk ordinance.

4 *Results in White and Colored Children* A summary of the data on white and colored children is given in table 4.

TABLE IV
Comparison of Skin Sensitivity in White and Colored Students

Color	Persons Tested	Positive Reactors	
		Number	Percentage
White	6005	611	10.1
Colored	1117	31	2.7
Total	7122	642	9.0

Two and seven-tenths per cent of 1117 colored children were sensitive to brucellergin and 10.1 per cent of 6005 white children. The colored students tested were all in junior and senior high schools. The difference between the two races is, therefore, more marked than these figures indicate because 1213 of the 6005 white students tested were under 10 years of age, the age group with a lower percentage of positive reactors.

5 *The Possible Relation to Milk Supply* The marked difference found in the numbers of positive reactors in the colored and white populations may be due to differences in their dietary habits. Ninety-eight and eight-tenths per cent of the raw milk sold in the city is used by the whites and 1.2 per cent by the colored population, although the latter constitutes 16.31 per cent of the total population. The daily per capita consumption of milk (exclusive of cream and buttermilk, both of which were negligible) averaged 0.211 pints in the colored group as compared with 0.521 pints consumed by the whites. Furthermore, 92.9 per cent of the milk consumed in the colored areas was pasteurized, and canned milk was a very popular item of the diet. Only 49.4 per cent of the milk consumed by the white population was pasteurized. The milk supply was verified in families in which there were children with positive reactions. This was possible in 614 of the 642 positive reactors. The results are tabulated in table 5.

Four hundred and eighty-seven, or 79.3 per cent of the persons with positive skin tests used raw milk. Since milk is commonly bought in grocery stores and the source of supply may change without the knowledge of the consumer it is difficult to state with certainty that a given family

TABLE V

The Type of Milk Consumed by 614 Persons with Positive Skin Tests

Milk Used	Number Cases	Percentage
Raw	487	79.3
Pasteurized	125	20.3
Canned	2	0.4
Total	614	100.0

used raw or pasteurized milk exclusively. The data are also complicated by the fact already mentioned that some of these children were directly exposed to animals. However, it appears that there is some relationship between the milk supply and percentages of positive reactors.

6 *The Relationship of the Results of Brucellergin and Tuberculin Tests*

The relationship of brucellosis and tuberculosis, both occurring in chronic and latent forms, and both related epidemiologically to bovine sources, presents interesting similarities. Here it is pertinent to present briefly only the results of the two specific skin tests, simultaneously performed.

TABLE VI

Relationship of Hypersensitivity to Tuberculin and Brucellergin in 7,122 Children

Result of Test		Number of Persons
Tuberculin	Brucellergin	
+	+	132
-	+	510
+	-	1864*
-	-	4616

* Personal communication from Dr. Clifton Hall of the Kansas State Department of Health.

The results indicate that there is no correlation between positive brucellergin and positive tuberculin reactions. In colored schools in which the percentages of brucellergin reactions were the lowest, the percentages of positive tuberculin reactions were among the highest found (45.0 and 62.8 per cent). In other schools though the differences were not so striking, the same lack of correlation was apparent.

7 *The Clinical Picture in the Sensitive Subject* An analysis has been made of the clinical symptoms in the positive reactors.²⁶ The results of this study confirmed our belief that many of these children had chronic complaints which were probably due to the ambulatory type of brucellosis.

SUMMARY

Simultaneous intradermal tests on adults with vaccine and brucellergin indicated that heat-killed vaccine produces more severe reactions than brucellergin. In all of the 13 cases investigated skin testing was followed by a rise in titer of specific agglutinins.

Intradermal tests with brucellergin in 7122 school children gave the following results

- 1 Positive reactions were found in 90 per cent
- 2 There was an increasing percentage of positive skin reactors in successive age groups up to early adulthood
- 3 Differences in reactions of males and females were found only in the 15-19 year old group and then only in white children
- 4 The lowest percentage of positive reactions was found in the colored children
- 5 Seventy-nine and three-tenths per cent of the positive reactors consumed raw milk
- 6 There was no correlation between positive brucellergin and positive tuberculin reactions

REFERENCES

- 1 FLEISCHNER, E C, and MEYER, K F The bearing of cutaneous hypersensitiveness on the pathogenicity of the *Bacillus abortus bovinus*, Am Jr Dis Child, 1918, xvi, 268-273
- 2 BURNET, ET Recherches sur la fièvre méditerranéenne III Diagnostic de la fièvre méd par intradermoreaction, Arch de Inst Pasteur, 1922, ii, 127-201
- 3 FAVORITE, GRANT O, and CULP, C F The intradermal test in undulant fever, Jr Lab and Clin Med, 1935, xx, 522-526
- 4 GOLDSTEIN, J D, FOX, W W, and CARPENTER, C M The recovery of *Brucella abortus* from the stools of healthy carriers, Am Jr Med Sci, 1936, cxc, 712-715
- 5 GIORDANO, A S *Brucella abortus* infection in man, Jr Am Med Assoc, 1929, xciii, 1957-1958
- 6 HUDDLESON, T F, JOHNSON, H W, and HAUMANN, E E A study of opsonocytophagic power of the blood and allergic skin reaction in brucella infection and immunity in man, Am Jr Pub Health, 1933, xxiii, 917-929
- 7 GOLDSTEIN, J D Cutaneous reactions in the diagnosis of undulant fever, Jr Clin Invest, 1934, xiii, 209-218
- 8 LEVIN, W The intradermal test as an aid in the diagnosis of undulant fever, Jr Lab and Clin Med, 1930, xvi, 275-281
- 9 KELLER, A E, PHARRIS, C and GAUB, W H Diagnosis of undulant fever The opsonocytophagic, allergic, and agglutination reactions, Jr Am Med Assoc, 1936, cvii, 1369-1374
- 10 MCBRYDE, A, DANIEL, N C, and POSTON, M A Brucella infection in children, Jr Pediat, 1934, iv, 401-405
- 11 JOHNS, E P, CAMPBELL, F J H, and TENNANT, C S A serological and clinical investigation of individuals exposed to *B abortus*, Canadian Med Assoc Jr, 1932, xxvii, 490-497
- 12 HEATHMAN, L S A survey of workers in packing plants for evidence of brucella infection, Jr Infect Dis, 1934, lv, 243-265
- 13 HUDDLESON, I F, JOHNSON, H W, and HAMANN, E E A study of brucella infection in swine and employes of packing houses, Jr Am Vet Med Assoc, 1933, lxxxiii, 16-30
- 14 MEYER, K F, et al The heterogenous infection chains as occupational diseases, Arch f Gewerbepath u Gewerbethg, 1934, v, 501-582
- 15 MEYER, K F, and GEIGER, J C The increasing importance of brucellosis as an occupational hazard, Jr Am Vet Med Assoc, 1935, lxxxvi, 280-286
- 16 MOLINELLI, E A La infección profesional de brucella en algunos ambientes urbanos y rurales de la República Argentina, La Semana Medica, 1934, ii, 124-158

- 17 BAUMGARTNER, L The relationship of age to immunological reactions, Yale Jr Biol and Med, 1934, vi, 403-434
- 18 HUDDLESON, I F Brucella infections in animals and man, Commonwealth Fund, 108 pp, 1934
- 19 DUBOIS, C and SOLLIER, N (1) Sur l'emploi de l'intradermoreaction a la melitine chez les sujets atteints de fièvre ondulante et chez les sujets sains vivants en milieu contaminé de melitococcie animale, Compt rend Soc de Biol, 1930, cv, 191-193 (2) Valeur de l'intradermoreaction a la melitine comme procede de diagnostic de la fièvre ondulante et de recherche des états d'allergie et d'immunité a l'égard du *B melitensis*, Ann Inst Pasteur, 1931, xlvii, 311-331
- 20 TAYLOR, R M, LISBOUNE, M, and VIDAL, L F Mouvement sanitaire, 1935, xii, 51-90
- 21 POSTON, M A, and THOMASON, R H Meningitis due to brucella in a child, Am Jr Dis Child, 1936, lii, 904-905
- 22 VEDEL, P A, and JANBON, M Deux cas de polyneurite melitococcique, Bull de la Soc des Sci Med et biol de Montpellier et du Languedoc Med, 1926, vii, 406-410
- 23 CARPENTER, C M, BOAK, R, and CHAPMAN, C D The significance of *Brucella abortus* agglutinins in human serum, Jr Immunol, 1929, xvii, 65-83
- 24 EVANS, A E, ROBINSON, F H, and BAUMGARTNER, L Studies on chronic brucellosis IV An evaluation of the diagnostic laboratory tests, U S Public Health Reports (In press)
- 25 EVANS, A C Studies on chronic brucellosis II Description of techniques for specific tests, Pub Health Rep, 1937, lii, 1419-1427
- 26 ANGLE, F E, ALGIE, W H Chronic brucellosis (undulant fever), an analytical study of the positive reactors among school children, ANN INT MED (To be published)

SYPHILIS AND GONORRHEA AS PUBLIC HEALTH PROBLEMS¹

By JOHN L. RICE, M.D., Commissioner of Health, *New York, N. Y.*

THE basic principles of a syphilis and gonorrhea control program are essentially the same for all communities. Differences may exist in the manner of administration and in the volume of service performed, but the problem of controlling these diseases and its solution are common to both urban and rural localities. Our main interest is in the reduction and, we dare hope, the eventual eradication of these diseases from our population.

Two fundamental aims of a control program are, first, the discovery of cases of syphilis and gonorrhea, and, secondly, placing them under medical care at least until they are no longer infectious. The approach to these objectives depends largely upon the characteristics of the local population and the resources of the community. Ideally, the burden of the diagnosis and treatment of these infections should be assumed by family physicians, or, where it is more desirable, by specialized private practitioners. Frequently, however, economic and social conditions make such an arrangement impracticable. The impoverished condition of many infected persons, who are a potential menace to the community, and the lack of cooperation in others make it necessary for an official agency to share the difficulties of the medical profession, or, occasionally, to invoke the power granted it by law to protect the health of the general population.

As we have amply demonstrated in New York City, it is entirely possible for the medical profession and the Department of Health to function in harmony and to their mutual advantage in the attack on these diseases. I should like to consider briefly, step by step, the essential points in our control program, determined by the needs of the City, and our accomplishments as far as they can be ascertained.

In the latter part of 1935, when our present extensive and intensive campaign against syphilis and gonorrhea was launched, widespread educational measures were adopted. Local newspapers and periodicals joined forces with the Department of Health in urging every one to be examined by a competent physician, and, where necessary, to take treatment. The favorable effect of this publicity is evidenced by the great numbers of telephone and personal requests for advice made to the Bureau of Social Hygiene immediately following each news release. To meet the public demand for information, the Department of Health has utilized all accepted media for the dissemination of knowledge including lectures, film showings, exhibits, and the distribution of posters and pamphlets. During the past year,

¹ A clinical lecture at the Department of Health in connection with the Twenty-Second Annual Session, American College of Physicians, New York, N. Y., April 8, 1938.

283 lectures and film showings were given to audiences numbering 27,000 persons of diverse social, religious, educational, and family groups

Professional interest has kept pace with heightened public interest, and, to meet the need that exists in the medical profession for additional training, the Department of Health has made available facilities for instruction. Graduate and undergraduate courses, for groups of 16 to 24 persons at a time, have been given in clinical and public health aspects of venereal disease control. Furthermore, isolated lectures totalling 60 were given in 1937 to professional audiences numbering 6,200. Staff conferences were held periodically during the year, in which outstanding medical authorities participated as guest speakers. These activities are not only informative but furnish an incentive to improved professional performance.

In addition to this general arousing of public and professional interest, more specific methods of discovering cases, and placing and retaining them under medical care were incorporated in our activities. In all its contacts with groups and individuals, the Department of Health, with the aid of the press, has emphasized the desirability of seeking advice and aid from private physicians. The five county medical societies had supplied the Department with lists of physicians competent and willing to diagnose and treat syphilis and gonorrhea at reduced fees, patients are being referred to these doctors at the rate of about 720 a year. As a further aid to keeping patients under the care of their private physicians and clinics, the Department is utilizing Social Security funds to distribute to doctors, free of charge, drugs for the treatment of their syphilis cases. In 1937, about 1,500 doctors and 28 hospitals were supplied with almost 250,000 doses of drugs for about 15,000 patients.

Educational and case-finding activities are centralized under an assistant director in charge of education and epidemiology and four medical epidemiologists. Their functions include, among others, the investigation of sources of infection and contacts of early syphilis cases as well as conferring with private physicians on problems of diagnosis and treatment of their patients. During the year 1937, 745 physicians were visited and 254 sources of infection, contacts, and delinquent cases were brought under the care of these private doctors through the efforts of our epidemiologists. They investigated 434 named possible sources of infection during the year, and of the total, 30 per cent were proved sources of infection. Considering the heterogeneous and rapidly shifting population of New York City, this is considered a creditable record.

As an indispensable counterpart of case-finding activities, a follow-up service must be integrated into a well-rounded syphilis and gonorrhea control program. Cognizance must be taken of the fact that some patients will lapse treatment regardless of attempts to impress upon them the necessity for regular attendance. Precautions should be taken immediately upon commencing treatment to help the patient, where difficulty exists, in removing obstacles which prevent him from continuing regularly under

medical supervision Where a patient is under the care of a private physician, this function is most satisfactorily assumed by the doctor In clinics, where a more impersonal relationship must necessarily exist, a specially trained social service staff should be assigned to this task

However, personal problems often make it necessary for a patient to discontinue treatment When the patient of a private physician is delinquent, the doctor may request the service of a Health Department nurse epidemiologist to follow up the case for him and under his supervision The same service is rendered to private clinics whose staff is inadequate for this purpose This function, as well as the investigation of some sources of infection and contacts, is assigned to a group of eight nurse epidemiologists under the supervision of an assistant director

During the first quarter of 1938, nurse epidemiologists made 1,740 visits to 943 lapsed cases, sources of infection, and contacts of private physicians and clinics Of these, 694 were new referrals The number of referrals from private physicians and clinics rose 62 per cent from 391 in the last quarter of 1937 to 632 in the first quarter of 1938 The use of this service by private physicians and clinics is expanding as they become increasingly familiar with the facilities offered them

The follow-up for Health Department clinics is being performed by a group of W P A social workers under the supervision of an experienced assistant Bureau director During the first quarter of 1938, these social workers made 8,624 visits to 6,287 lapsed cases and returned 3,941, or 63 per cent to treatment

I have considered briefly the measures taken by the Department of Health to discover cases of syphilis and gonorrhea, place them under medical supervision, and to return them to treatment when they are delinquent In order to round out a well-balanced program, it is necessary to provide diagnostic consultation and treatment facilities for persons unable to defray the usual expense

The Department of Health maintains an extensive laboratory service for the examination of blood and spinal fluid specimen for syphilis, and smears for gonorrhea Fifty-four per cent of the specimens received in the laboratories are sent by private physicians In 1937, over 430,000 blood and smear specimens were examined, this figure represents an increase of 25 per cent over the preceding year

At strategic points throughout the City, where the need is most acute, are located 20 centers offering diagnostic and consultation services for private physicians and clinics When a patient is unable to afford the usual fee for examination, or when it is desirable to have a diagnosis confirmed, or when a consultation is needed, private doctors and clinics are at liberty to use these services During the year 1937, more than 20,000 examinations of various kinds were performed at these clinics for patients of private physicians and clinics

Following examination, whenever it is necessary for a patient to be treated, every effort is made to have him continue under the supervision of his family physician or under the care of a doctor recommended by the county medical societies. If this arrangement is impracticable, an attempt is made to send him to a private clinic. If neither of these alternatives is acceptable, the patient is registered at one of the 21 treatment services maintained by the Department of Health. This procedure, as a short statistical analysis will indicate, has proved to be quite satisfactory.

At the end of 1937, the Bureau of Social Hygiene was operating 130 clinic sessions each week (there were 92 at the end of 1936 and 49 at the end of 1935). The most interesting phase of clinic service is that although the number of cases examined during 1937 increased 36 per cent over the preceding year to a total of 67,260 cases, the individuals accepted for treatment increased only 11 per cent in that period. More than three times as many cases were referred by the diagnostic service to private physicians for treatment in 1937 as compared with 1936, the number of referrals to private clinics in that period was almost doubled. The number of patients referred to Health Department clinics for treatment decreased 4 per cent.

Visits to the treatment service increased by 24 per cent, from 350,000 in 1936 to about 430,000 in 1937, although the number of patients registered for treatment increased by only 11 per cent. This fact indicates that clinic patients are now being retained under treatment more effectively than in the past.

In addition to the routine services I have outlined, several projects in medical research and in public health methods in the control of syphilis and gonorrhea are being carried on. The importance of such projects lies not only in the facts which are brought to light but in the stimulating influence they have on the staff of the Bureau and others who are interested in the subject of syphilis and gonorrhea control. Some of these projects are being financed by private funds. The more interesting demonstrations include a project limited to Staten Island which has for its purpose the development and study of educational, diagnostic, and epidemiological case-finding methods as applied both to syphilis and gonorrhea. Measurements will be taken from time to time to determine the results of various methods.

In November 1937, funds were made available for further experiment with the massive arsenical treatment of syphilis by the so-called "continuous-intravenous-drip methods" of administering arsphenamine. The details of this study have been planned by a committee of distinguished syphilologists and internists.

Since January 1937, the Bureau of Laboratories and the Bureau of Social Hygiene have been jointly conducting an important clinical and laboratory study of the gonococcus.

These three projects are representative of the interest and participation of the Department of Health in experimental work connected with problems of the control, diagnosis, and treatment of syphilis and gonorrhea.

To recapitulate, the Department of Health is following basic principles, generally accepted as being universally effective in the control of venereal diseases

The chief elements in the program are

- 1 Case-finding activities to include
 - (a) Popular education,
 - (b) Epidemiological investigation
- 2 Easily available diagnostic services for the general population
- 3 Treatment services for low income groups
- 4 Follow-up services to retain patients under treatment at least until they are non-infectious
- 5 Professional education both for practicing physicians and for undergraduate medical students
- 6 Facilities to aid private physicians and clinics in keeping patients under their treatment including
 - (a) Consultation services,
 - (b) Free drugs,
 - (c) Follow-up service

The success of these measures has, as I have briefly indicated, been encouraging enough to predict that, if the same course of action is followed over a number of years, always with necessary changes to meet current needs, substantial progress will be made in the eradication of syphilis and gonorrhea in New York City

SYSTEMIC REACTION TO ORAL FUSO-SPIROCHETOSIS WITHOUT LOCAL LESIONS^{*}

By WILLIAM H. BARROW, M D , F A C P , *San Diego, California*

ORAL spirochetes and fusiform bacilli were first identified in the 1890's as the pathogenic organisms in ulcero-membranous diseases of the mouth and throat. The work of Veillon, Plaut, and Vincent was quickly confirmed by others and thereafter fusio-spirochetal angina and stomatitis were seldom mentioned in the literature except in connection with some unusual or interesting complication or with reference to some new form of treatment. The disease has been called *Vincent's angina* or *Vincent's infection*, *ulcero-membranous gingivitis*, *trench mouth*, and *spiro-fusillary gingivitis*. As the nomenclature would indicate the disease has been and is described as being characterized by ulceration or pseudo-membrane formation in the mouth or throat, and even the mildest forms as presenting a definite gingivitis with small ulcerated areas at the gingival margins. In a recent comprehensive monograph on oral spirochetes Smith¹ states that pyorrhea and periapical infection may sometimes be caused by fusio-spirochetal organisms, but even here dental or periodontal pathologic lesions are easily demonstrable. Systemic and constitutional symptoms of anorexia, lassitude, cervical adenitis, fever, leukocytosis or pseudo-leukemic dyscrasias are described but only as secondary to the local lesions. The purpose of this paper is to report what appears to be a clinical manifestation of the infection without the characteristic local signs. Although doubtless recognized by many physicians and dentists this form of the disease has not, to my knowledge, been described in the literature.

TABLE I
Symptoms in Order of Frequency

- 1 Malaise, loss of weight, nervous irritability
- 2 Indigestion, anorexia
- 3 Aching in muscles of shoulders or neck
- 4 Soreness or aching of throat without objective findings
- 5 Transient dull red infiltration of buccal mucous membranes, especially of lips
- 6 Urticaria
- 7 Sensitiveness of teeth with gross or roentgen-ray findings negative
- 8 Anemia
- 9 Cervical adenitis, "soreness of mouth," angioneurotic edema, gingivitis, fever

In table 1 are tabulated in order of their frequency subjective and objective symptoms which seem to fit into a definite syndrome pattern. In patients with this symptom complex and where a smear from the gingival margins and from between the teeth revealed spirochetes and fusiform bacilli in abundance treatment effected a disappearance of the organisms and usually brought about relief from symptoms. A recurrence of the bac-

^{*} Read before the General Medicine Section of the California Medical Association at the sixty-sixth annual session, Del Monte, May 2-6, 1937

terial invasion was accompanied by a return of the symptoms in whole or in part

In practically all the cases there were complaints of malaise, loss of weight, mental depression, and nervous irritability. The usual causes for psychasthenia were not demonstrable. Intestinal indigestion and loss of appetite were common. The symptoms, however, did not suggest organic disease and gastrointestinal studies were negative. Quite characteristic was a cervico-occipital neuralgia, described as an aching between the shoulders and in the muscles of the neck posteriorly. As common a complaint was an aching in the throat, often with definite spots of soreness to which the patient could point but where careful examination failed to reveal any lesion. A patient with this as the predominant symptom was apt to make his way from one otolaryngologist to another being told in one office that he had "a little sinusitis," in another that he was a psychoneurotic, but himself convinced that nothing could hurt like that without there being something that could be seen. Next in order of frequency was a transient dull red infiltration of the buccal mucous membrane especially of the lips and roof of the mouth. A patient would display this phenomenon with some satisfaction as evidence of the fact that here at last was something that anyone could see, visible proof that his complaints were not all imaginary. This symptom was usually erroneously attributed by the baffled attending physician to over-medication or to a vitamin deficiency. A few of the cases developed urticarias, the possible significance of which will be discussed later. Only about a third of this series of patients complained of any symptom referable to the teeth or gums and this was characteristically a sensitiveness to pressure and to heat and cold. Except in two cases where there was a very mild gingivitis, examinations by competent dentists failed to reveal any demonstrable lesions. It is significant that even when the diagnosis had been established by the finding of Vincent's organisms in great excess in the mouth, it was often difficult, because of the absence of any visible inflammatory reaction to convince the patient's dentist that this could be the etiological factor or that treatment was indicated. As might be expected, a mild secondary anemia occurred in a few cases. There was no leukocytosis such as is often seen in the more severe typical Vincent's infections.

In table 2 the incidence of these symptoms is indicated graphically in a series of 14 patients.

Case 1 presented all the symptoms that have been described except urticaria. In a position to receive the best of medical attention she was studied thoroughly and for two years it was believed that a psychoneurosis was the most probable explanation of her symptoms. Roentgen-rays of the sinuses, teeth, gall-bladder, and gastrointestinal tract were negative. Except for a mild secondary anemia all laboratory findings were normal. Repeated nose and throat examinations were essentially negative. The gums were normal in appearance, free from pyorrhea, and dental examinations were negative. Finally two years after the onset of symptoms there appeared several small ulcers on the pharyngeal wall and buccal mucous membrane which suggested the possibility of a Vincent's infection. Smears from between the

teeth and under the gingival margins revealed the fuso-spirochetal organisms in large numbers. Treatment of the mouth with salvarsan and the oxidizing agents and general treatment with bismuth and neoarsphenamine brought about an immediate remission of symptoms. Recurrences, however, necessitated further treatments until the patient herself called attention to the fact that these recurrences always took place at home, never when she was out of town. Examination then of the rest of the household revealed a carrier (without symptoms) in the person of a maid. With her dismissal permanent recovery was effected.

Case 2 presented all the symptoms previously enumerated except the cervical neuralgia. Her outstanding complaints, however, were a persistently recurring urticaria and a sensitiveness and feeling of looseness of the teeth. In spite of this latter symptom examinations by competent dentists had failed to reveal any demonstrable dental or periodontal pathologic lesions. Diagnostic studies by two Eastern internists were essentially negative. Skin tests indicated sensitivity to certain foods.

TABLE II
Cases and Symptoms

Symptoms	Cases Sex and Age													
	I F-40	II F-35	III F-42	IV F-41	V F-48	VI F-47	VII F-46	VIII F-45	IX M-45	X F-60	XI M-55	XII F-50	XIII M-48	XIV M-40
Malaise loss of weight etc	+	+	+	+	+	+	+	+	+	+			+	+
Indigestion anorexia	+	+	+	+			+			+	+	+		+
Occip cervical neuralgia	+		+	+	+	+						+	+	
Aching of throat	+	+	+	+		+			+		+			
Redness buccal mucous membranes	+	+			+		+		+					
Urticaria		+			+	+		+				+		
Sensitive teeth	+	+						+					+	
Secondary anemia	+	+	+			+	+							
Miscellaneous	Fever	Aggravated with menses	Fever	Adenitis Ang neur edema	Aching mouth Ang neur edema			Gingivitis		Smarting of mouth	Buccal patches Adenitis		Gingivitis	

but elimination diets gave no relief. On empirical grounds she was treated for a possible faulty calcium metabolism without benefit. It was suspected that this patient's symptoms also were possibly neurogenic in origin. It was only after protracted treatment along these and other lines that a smear was taken from the mouth and a three plus Vincent's infection discovered. This patient was resistant to treatment and although receiving immediate partial relief required several courses of bismuth and neoarsphenamine before recovery was effected. She now reports that she has occasional exacerbations which are easily controlled by local treatment.

Case 3 is the only one of this series which, presenting most of the cardinal symptoms and found to have a two plus Vincent's infection, failed to improve subjectively although the organisms were, as far as could be judged by a smear, eliminated from the mouth. One can only draw the conclusion that the finding of the organisms in a suspected case points to a possible and not to a positive diagnosis.

Cases 4 and 9 are of interest because complaining of their throat symptoms they both for long periods of time sought relief at the hands of otolaryngologists who found no evidence of pathology. It was only when, finally, smears for Vincent's were found to be positive and appropriate treatment was instituted that relief was obtained.

Five cases had urticarias which were relieved or alleviated by treatment after the infection had been demonstrated. In only three of the fourteen cases were there any gross demonstrable lesions of the gums or mucous membranes that might be said to be even suggestive of Vincent's infection. Case 11 had a few small patches on the buccal mucous membrane and a mild cervical adenitis, and cases 8 and 13 had a gingivitis without ulceration or membrane formation. It was only in these last two that the patients complained of any inflammation or irritation of the gums and their inclusion in this series is perhaps warranted on the basis that the other subjective symptoms coincided with those of cases showing no such tell-tale signs, thereby indicating a probable common etiological factor.

The *Treponema vincenti* and the fusiform bacillus in common with other oral spirochetes, spirilla, vibrios, leptothrices, and cocci, are found in small numbers in the mouths of normal individuals. Miller and Epstein² in 1926 reported results of smears taken from the gingival margins of 160 mouths in which there was no gross evidence of disease. Spirochetes were absent in only 23 per cent and the fusiform bacilli in only 7 per cent. The organisms were few in about 40 per cent, numerous in about 30 per cent, and very numerous in as many as 10 per cent. They mention other investigators who reported 50 per cent positive smears from apparently normal gingival margins and the finding of fusiform bacilli and spirilla (spirochetes?) in excised tonsils. Obviously then fuso-spirochetal organisms are opportunists rather than primary pathogens, producing characteristic lesions only when favorable conditions for incubation cause them to multiply. Classification of a smear as positive calls for experience and conservatism. Figure 1 showing an occasional spirochete and bacillus is the usual and normal finding. Figure 2 with frequent spirochetes and a few bacilli (a two plus smear) is of possible significance if supported by other clinical signs. Figure 3 with masses of spirochetes and many bacilli is distinctly pathological. The presence of numerous leukocytes in any smear is highly suggestive of an inflammatory reaction even if the gums appear normal. Using this standard as a rough index of the smears from this series of cases, eight were three plus and six were two plus.

Care and thoroughness should be exercised in obtaining the smear. In view of the fact that these organisms are anaerobes a swab wiped over the gingival margins is obviously inadequate. We have used a small platinum loop which is introduced between the teeth and as far under the gingival margins as possible without trauma. It is important that smears should be taken from around and between all the teeth, it being not uncommon to find severe infection in only one part of the mouth.

The question arises as to why the same degree of infection, as indicated by smears, should cause ulcero-membranous gingivitis in one individual, only constitutional symptoms in another, and perhaps no demonstrable reaction in a third. In the case of the mouth lesions any factor that tends to reduce the resistance of the tissues favors the formation and spread of an ulcero-membranous gingivitis. In addition to this is it not possible that there may be much individual variation in a patient's sensitivity to the soluble bacterial toxins or the endotoxins (transient products of microbial proteolysis) and in the character of his manifestation of this sensitivity? The unusually high



FIG 1 Smear from normal mouth showing occasional spirochete and a few fusiform bacilli
(1×1000)

incidence of urticaria in this series might well be evidence of such a phenomenon in these patients. One might advance the theory that there are a few individuals, who with minimal local lesions and maximal systemic symptoms, may be said to be Vincent's sensitive.

It is hardly within the scope of this paper to go into the details of treatment. Certain general principles may, however, be summarized. Fortunately the fuso-spirochetal organisms are arsenic sensitive. The use, therefore, of the arsenicals in local and general treatment constitutes a specific remedy. Bismuth preparations intramuscularly given either alone or in combination with the arsenicals are effective. Kolmer³ advocates the use

of bismarsen. The *T. vincenti* and the fusiform bacillus being anaerobes, the free and frequent use of oxygen producing agents, such as sodium perborate, is indicated.

Trauma of the gums should be avoided and it is, therefore, well to advise against the use of a tooth brush while the case is under treatment. For the same reason the patient should not, at this stage, be referred to the dentist for scaling of the teeth or other traumatizing procedures. After the infection has been eliminated or brought under control it is, of course, essential that the cooperation of the dentist be sought. Elimination of the so-called

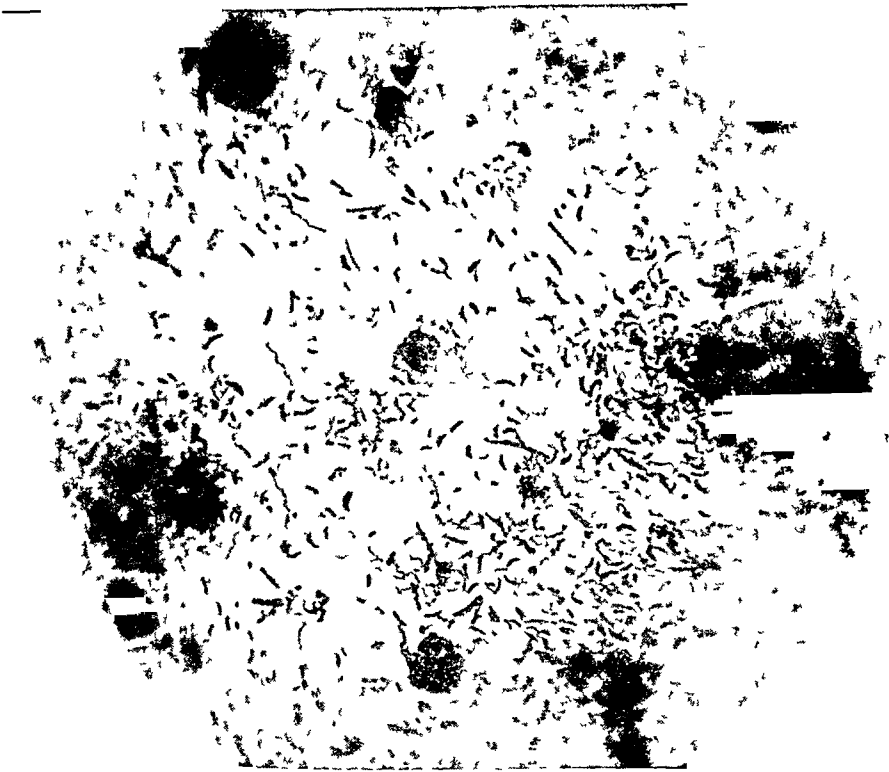


FIG 2 A two plus smear with numerous spirochetes and fusiform bacilli and a few pus cells (1 X 1000)

“zones of incubation” (abnormalities causing pocket formation or gingival irritation) is often necessary to effect complete recovery or to prevent recurrences. The elimination by the patient of any irritating agents is important. Recently vitamin C deficiency has been mentioned as a possible predisposing factor and this should be ruled out or a vitamin concentrate be given on empirical grounds. Finally the patient's intimate associates should be examined as possible carriers. The Vincent's organisms apparently stimulate no antibody formation. The disease is not, therefore, self-limited and there is no acquired immunity. Susceptible patients consequently require the protection of every possible prophylactic measure.

In the cases reported in this series local treatment alone was prescribed or administered in three and local and general treatment in nine. The teeth were extracted in one case and one case (seen in consultation) was not followed. Of the 14, ten recovered or were markedly relieved after treatment and one case was unimproved (Case 3 previously mentioned). The results in three cases are not known.

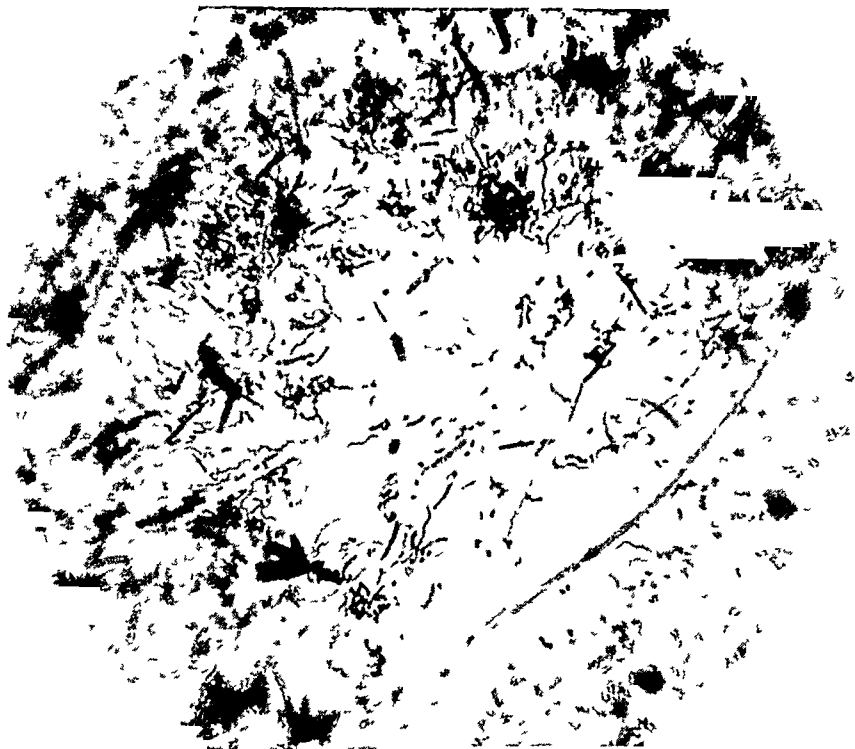


FIG 3 A three plus smear showing many fuso-spirochetal organisms (1×1000)

SUMMARY

1 Vincent's infection as generally described is characterized by an ulcero-membranous inflammation of the mouth or throat accompanied by mild systemic reaction. A series of cases is presented with minimal or no recognizable local lesions but with a definite symptom pattern indicative of infection and toxemia.

2 Smears from around the teeth showed moderate or heavy invasion of fuso-spirochetal organisms and treatment of this condition effected recovery in most of the cases.

3 Vincent's organisms are found in normal mouths so that the criterion of a so-called positive smear is only a comparative one. Care and proper technic in making the smear are essential to a reliable test.

4 The theory is advanced that this atypical manifestation of the infection occurs in individuals who are more than usually sensitive to the organisms.

5 The arsenicals are specific for the treatment of the infection and dental prophylaxis and the elimination of carriers from the patient's environment are necessary for the prevention of recurrences

REFERENCES

- 1 SMITH, D T Oral spirochetes and related organisms in fuso-spirochetal disease, 1932, Williams and Wilkins, Baltimore, Chapter 9-10
- 2 MILLER, H E, and EPSTEIN, NORMAN Vincent's angina The significance of fusiform bacilli and spirilla in mucous membrane lesions, California and West Med, 1926, *xxiv*, 633
- 3 KOLMER, J A Bismuth arsphenamine sulphonate (bismarsen) in the treatment of syphilis and of other spirochetic infections, Arch Dermat and Syph, 1930, *xxi*, 394

CEVITAMIC ACID (ASCORBIC ACID, CRYSTALLINE VITAMIN C), A CRITICAL ANALYSIS OF ITS USE IN CLINICAL MEDICINE ¹

By IRVING S. WRIGHT, A. B., M. D., F. A. C. P., *New York, N. Y.*

THE fact that cevitic acid can be chemically analyzed, synthesized and recovered from body tissues and fluids has resulted in a tremendous impetus being given to its study. Out of the work already reported (50 to 100 articles per month for the past three years) has emerged a mass of material made up of truths, errors and debatable questions of which the last mentioned group constitutes the major portion.

Four general statements may now be made, however, with reasonable certainty, as follows:

1. Most patients with scurvy can be cured with cevitic acid. A few seem resistant to this substance whereas they can be cured with large doses of lemon or other citrus fruits ¹.

2. Increased fragility of the capillaries when due to vitamin C deficiency will be restored to normal by the use of this substance, with the same exceptions ^{2, 3, 4, 5}.

3. Vitamin C deficiency may occur under a great variety of conditions even when the intake of this substance is apparently adequate. These include increased metabolism from infection (with or without fever) or other causes, interference with absorption or utilization because of achlorhydria, colitis or other intestinal disturbances and additional factors concerning which our present knowledge is limited. Deficiency inevitably occurs in man when the intake is inadequate since man is apparently unable to synthesize this substance and his storage capacity is very limited.

4. The proved indications for vitamin C therapy depend primarily on the presence or danger of a deficiency of this substance in the patient. This applies whether the primary problem is clinical or subclinical scurvy or any of the very numerous diseases for which it has been recommended as an important therapeutic aid.

The determination of the degree of deficiency of this vitamin in an individual has given rise to sharp differences of opinion and the presentation of numerous methods and modifications of methods. If one surveys this problem with a broad outlook toward future usefulness it becomes at once apparent that while some of these differences are important, many of them are largely academic.

A recent tendency has been noted to introduce new chemical methods and modifications of earlier methods for the study of vitamin C, which theoretically approach accurate results more closely by minute amounts.

* Presented before the American College of Physicians, New York, N. Y., April 8, 1938.

When, as is the case with certain of these, the procedures used introduce opportunities for errors as great or greater than those of the former techniques it appears that the originators are obscuring the situation rather than clarifying it

The primary purpose of this paper is, therefore, the presentation of a method of approach by which the degree of saturation or deficiency of vitamin C can be determined for clinical purposes. The procedures recommended are mentioned not because they are the only possible methods or because they represent the ultimate but because they have stood well in comparative tests against all other methods, both in our laboratory and other unbiased laboratories. It is expected that improvements will be forthcoming during the next few years.

Probably the simplest procedure giving the maximum amount of information is a single determination of cevitamic acid in the blood plasma. Numerous chemical methods for this have been advocated but we have found the macro method of Farmer and Abt⁶ to be very satisfactory. Pijoan and Klemperer⁷ introduced a modification of this method using potassium cyanide. Comparative studies of the two techniques in our laboratory showed this modification to be unnecessary if the determinations were to be made within 30 minutes but helpful if the blood was to stand four hours or more. The intermediate time zone produced variable results. The normal blood plasma level for cevitamic acid in adults lies between 0.7 and 1.3 mg per 100 c.c.

This test might be compared to a single blood sugar test. It gives a general idea of the status at the moment of taking the specimen but may have been affected considerably by intake or deficiency of vitamin C during the preceding 24 to 48 hours, or by other factors such as renal retention⁸.

Single urinary specimens may vary so widely in content of cevitamic acid as to be valueless and 24 hour specimens have certain disadvantages as follows

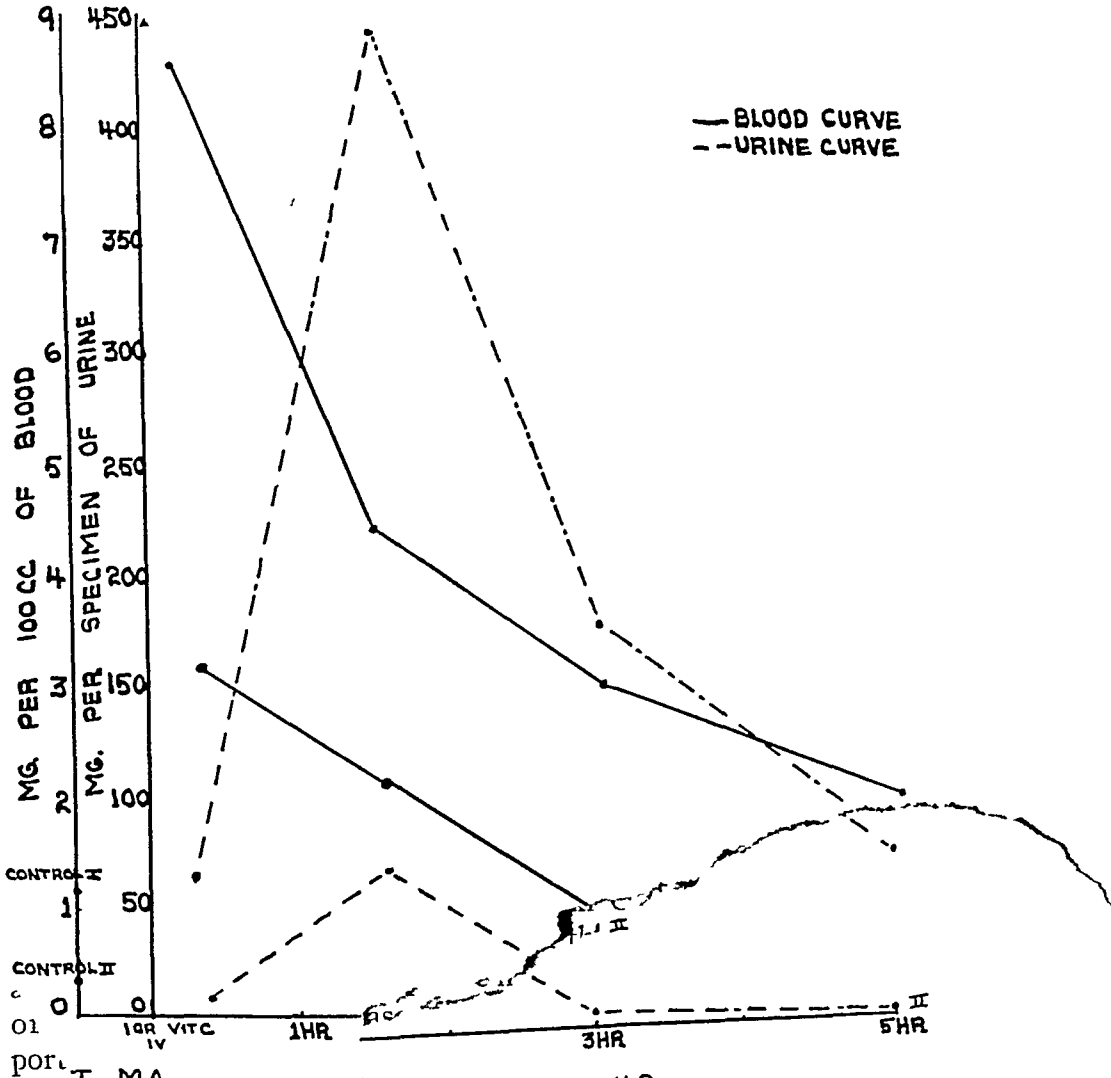
A Individual specimens must be analyzed immediately upon voiding or carefully preserved by being acidified to pH₃ with sulphuric or acetic acid and kept in the dark at ice box temperature⁹. Even under these conditions a loss of over 12 per cent may occur in 24 hours.*

B Twenty-four hour specimens are difficult to secure without loss from ambulatory patients or indeed any but the most cooperative hospital patients.

The obvious solution of this situation was the use of a test dose method. At first doses of 300 to 1000 mg. were given orally^{11, 12, 13, 14}. The normal return was considered about 30 per cent in 24 hours, but the possibility of uncertain absorption or utilization from the intestinal tract under certain

* Fleming and Burrows¹⁰ have reported that sulphuric acid destroys ascorbic acid rather than protecting it but for practical purposes we have found its use satisfactory. Our studies do not confirm their extreme statements of rapid destruction by sulphuric acid. We have found sulphuric acid preferable to acetic acid when used in the test dosages. Immediate determinations are to be preferred.

conditions indicated the need for an intravenous route of administration. Accordingly we suggested^{9, 15} a test dose of 1000 mg intravenously. Normally at least 500 mg are excreted during the following 24 hours. We demonstrated that 80 per cent or more of the total urinary excretion in 24



I MA
T₁ DIAGNOSIS - NORMAL
DIETARY HISTORY - 1
1 HR URINARY EXCRETION - EXCELLENT
FOLLOWING 1000 MG VITAMIN C - 789 MG

II HR
DIAGNOSIS - DYSENTERY
DIETARY HISTORY - POOR
5 HR URINARY EXCRETION - 123 MG
FOLLOWING 1000 MG VITAMIN C

problem typical curves of vitamin C in the blood and urine in individuals with good and apparent the degrees of saturation. Following 1000 mg test dose intravenously

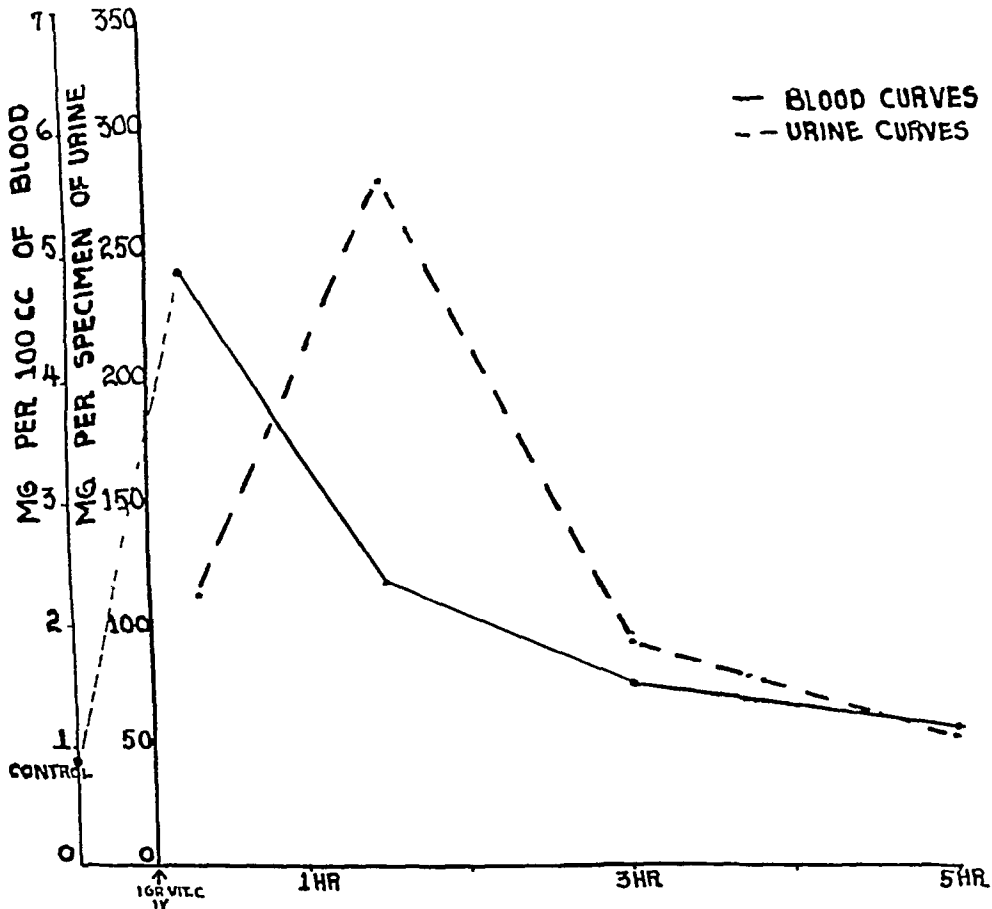
are largely ac

A recent procedure would be excreted in the first five hours. This and modification resulting in a five hour test which could be utilized theoretically app. Similar tests have been advocated using a smaller

vere carr

* Presented before Merck & Co., Inc., Rahway, N J

dosage (100 to 300 mg) These smaller doses are suitable for infants but have the following disadvantages *A* The factor of error of the chemical determinations including that of the endpoint reading is increased as the amount of vitamin C present is decreased *B* The effect of the immediately preceding dietary regime may influence the figures proportionately more markedly if the return is small (e g, 30 to 50 mg as compared with



C D DIAGNOSIS - GLOMERULO NEPHRITIS (NO NITROGENOUS RETENTION)
 DIETARY HISTORY - GOOD
 5 HR URINARY EXCRETION - 524 MG
 FOLLOWING 1GM CEBIONE

CHART II Typical blood and urine vitamin C curves in a patient with renal disease but no nitrogenous retention The curves are normal

300 to 500 mg) *C* The effect of the RSH compounds¹⁶ (interfering reducing substances such as glutathione, cysteine, etc) becomes proportionately less important with the increase in total figures We know of no evidence proving that increasing the test dosage produces an appreciable increase in the excretion of these factors

The test dose of 1000 mg does produce results which run parallel to certain other methods For example using the 100 mg test dose carefully

controlled, about 40 mg will be obtained as the average output in five hours as against 400 mg for the 1000 mg dose from a patient with similar saturation. As above pointed out, however, the larger dose tends to minimize the factors of error. It has been suggested that the large dose method may result in a spilling into the urine even when the body is unsaturated. That this is only in proportion to the saturation has been demonstrated since we

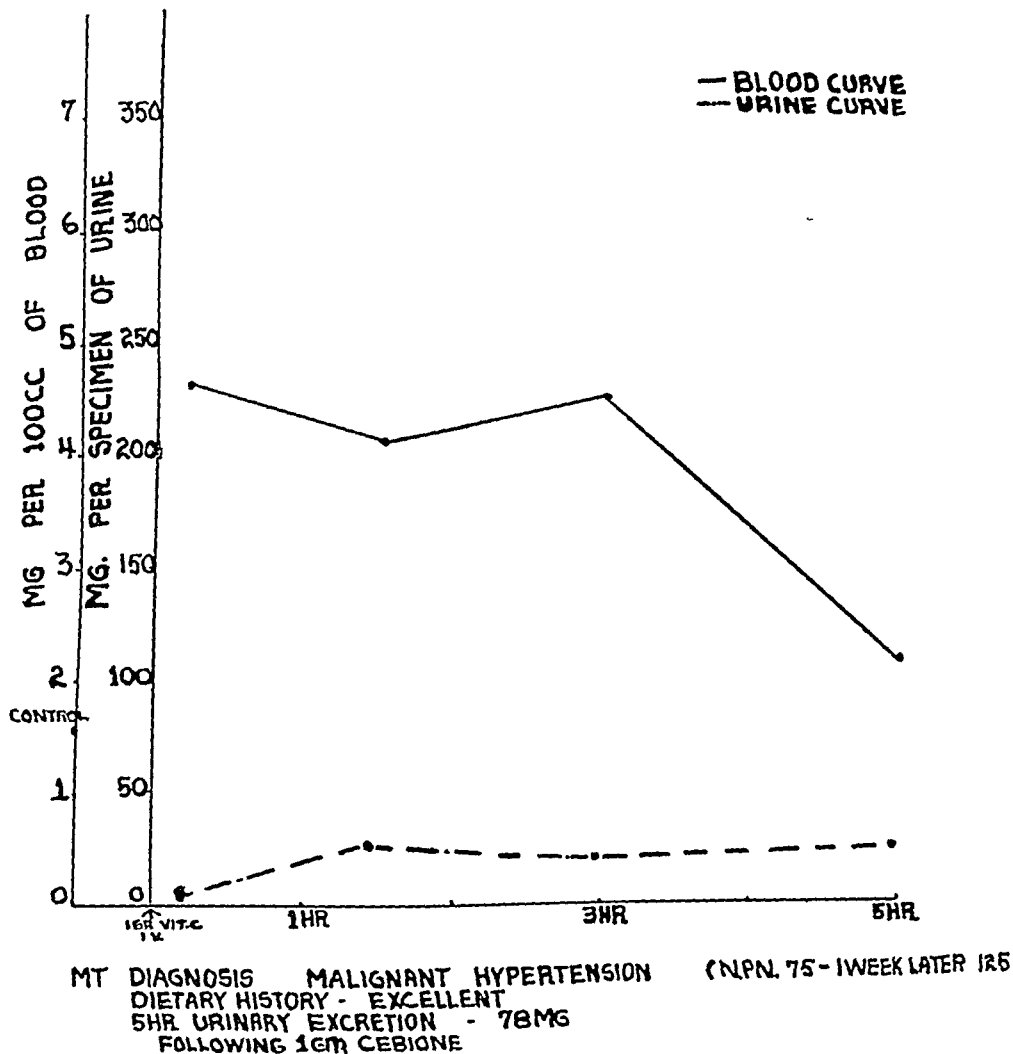


CHART III Blood and urine curves in a patient with malignant hypertension with nitrogenous retention. Note retention of vitamin C in blood with delayed excretion, or 78 mg in 5 hours. This does not occur in all patients with nitrogenous retention.

have had excretions as low as 42 mg in five hours while the blood level dropped to normal probably as a result of rapid utilization or absorption in unsaturated tissues. In saturated cases the return has been proportionately greater, up to practically 100 per cent. In most instances the above outlined determination of the five hour urinary excretion, using a modification of Tillman's dichlorophenolindophenol method, is adequate to establish

degree of saturation but recently we⁸ have demonstrated that in some patients with kidney disease and nitrogenous retention vitamin C retention may also occur. This may interfere with the excretion and hence the interpretation of results from any urinary study. In patients with kidney

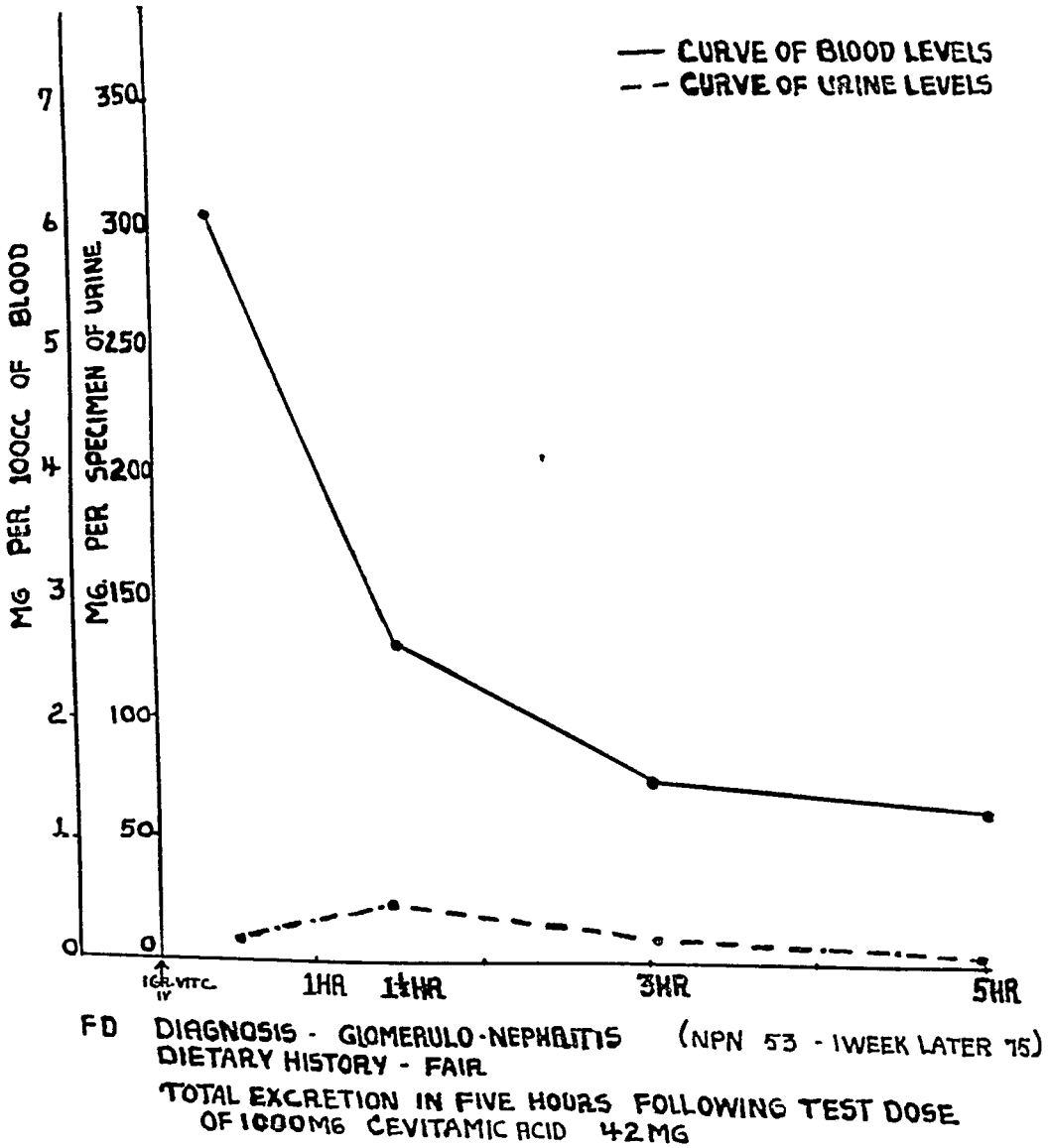


CHART IV Blood and urinary curves in patient with nitrogenous retention. Note that the blood curve dropped normally without appreciable increase in excretion. We would interpret this as indicating rapid utilization or storage by the body.

disease, therefore, a parallel blood and urinary study clarifies the picture as indicated by the accompanying illustrations.

In addition, one must consider in all chemical determinations other possible factors of error such as the effects of certain drugs, including the

salicylates¹⁷ (not definite) which produce an increased excretion and pyridium¹⁸ which produces a color affecting the endpoint determinations

We have followed the course of a large number of patients for periods up to two years checking the five hour urinary test against the clinical course of the disease and response to therapy, blood plasma studies and the capillary fragility tests^{4,9}. It has proved to be very helpful and satisfactory for general use. The exceptions to this have been noted.

Mention should be made of the intradermal test of Rotter¹⁹ later reported by Portney and Wilkinson²⁰ in which the dye dichlorophenolindophenol is injected into the skin and the length of time necessary for the disappearance of the color by oxidation timed. Saturated patients took less than five minutes, normals between five and 10 minutes, and deficient patients more than 10 minutes. Other factors than vitamin C may enter into the reaction but, if confirmed, it appears to have clinical value for rough estimations.*

The value of capillary fragility studies† has been challenged in some quarters. Certain factors have been chiefly responsible for this. 1 The workers expected results which were too exact for most biological tests. The difference of a few petechial spots is not very important but large differences are. 2 Too small an opening was used in a negative pressure type of apparatus. 3 Different areas of skin were used. The latter two factors when combined result in serious error because the potential number of minute vessels capable of rupturing may vary widely in different areas and hence affect the count considerably, especially if small areas are studied. Negative pressure methods require special apparatus, whereas every doctor has in his office adequate equipment to perform a satisfactory and informative capillary fragility test.

The procedure which we have used since 1934 in thousands of observations with very helpful results is as follows^{2,4,8}.

1 Place blood pressure cuff on upper arm and elevate the pressure to half way between systolic and diastolic readings, maintaining this level for 15 minutes. (If there is an excessive number of hemorrhages the time may be reduced to 7½ or 5 minutes.)

2 Two circles 2½ cm each in diameter are drawn on the inner smooth surface of the forearm, the upper edges of which should be 4 cm below the elbow crease. This obviates the great differences found at the elbow. Because of varying numbers of wrinkles, folds, etc., in different individuals, the distribution of the minute vessels is disturbed in that area.

3 Five minutes after release of the pressure the number of the petechiae readily seen with the naked eye are counted and an average taken as the

* Since presenting this paper we have carefully checked this method and found it unsatisfactory, the range of error being too great. Details will be published elsewhere (Wright, I S, and MacLenathen, E.)

† Although commonly known as capillary fragility or resistance studies they should more correctly be termed tests for the study of the fragility of the minute vessels of the skin including venules and probably arterioles.

figure Many new spots appear during the first few minutes after the release of the pressure

The normal response for adults is 10 or fewer per circle, the borderline zone is taken as 10-20 and above 20 is considered definitely pathological

4 This may be repeated every four days alternating arms, thus allowing adequate time for restoration of the ruptured vessels The negative pressure methods do have the one advantage that the tests may be repeated more frequently

This simple procedure, a modification of Gothlin's technic,²¹ used routinely will uncover a surprising number of individuals with pathological fragility of the minute vessels The fact that this is not always due to scurvy makes the observation none the less important In spite of all of our chemical procedures to determine saturation *fragility of the minute vessels still remains the first positive clinical evidence of the presence of the disease entity scurvy*

The fragility may also be increased in other conditions such as certain purpuras, in poisonings, such as those due to neoarsphenamine and carbon monoxide, by toxins, such as those of scarlet fever, subacute bacterial endocarditis, and diphtheria, and by metabolic products associated with anemia, acetonemia, menstruation and other conditions In many of these conditions increased fragility occurs as a preclinical sign and its presence should place the physician on his guard A clinical differential diagnosis is usually easily made The confirmation by chemical tests and a cure with cevitamic acid establishes the clinical diagnosis of scurvy On the other hand the chemical tests may be deceiving in this situation, since lack of vitamin C may quickly result in unsaturation without the development of scurvy for weeks or months and conversely a high vitamin C diet given to a patient with scurvy may produce a rapid chemical recovery while he still has clinical manifestations of the disease

One of the most important facts which has been established by all workers in this field is that scurvy, especially in its preclinical forms, is a very common disease among all economic classes It would be a safe generalization to make that practically every physician occasionally has had one or more of these cases pass through his office or clinic unrecognized Use of the capillary fragility test above described would have resulted in the recognition of most of these cases The symptoms of which these patients may complain vary enormously, including weakness, heaviness, pains in the legs and elsewhere, dizziness, nausea, dyspnea, bleeding from nose, mouth, rectum and bladder, easy bruising, and a host of others The signs are also of a most diverse nature, including bleeding of the gums, throat, nose, urinary and gastrointestinal tracts, purpuric spots and evidence of rupture of the vessels anywhere on the body surface including under the toe nails, the vessels of the sclerae and other unusual places, brawny pigmented edema of the lower legs and many other bizarre manifestations, practically all of

which depend directly or indirectly on rupture of the blood vessels. Roentgen-rays may show elevation of the periosteum from hemorrhage but in our experience this is rare in adults as we see the disease today.

In our series of more than 200 cases of definite scurvy we have seen five cases in doctors or their families and eight cases in nurses. More than 50 per cent of our patients could easily afford the preventive citrus fruits, many were wealthy and one owned a large orange grove. The causes of the disease aside from poverty were, distaste for citrus fruits and other food containing large amounts of vitamin C, allergic and gastrointestinal sensitivity to such foods, diets prescribed by physicians for the treatment of ulcers, colitis, urticaria and other conditions, faddist diets, winter diets and inability to utilize vitamin C when taken by mouth. Cases in these groups constitute one major established indication for the use of cevitic acid.

The list of diseases for which cevitic acid has been recommended is too long to permit a detailed discussion of each claim. Many have been mentioned in our previous reviews^{4, 8}. Only those which seem significant at present will be included in this paper.

While certain patients with low platelet counts seem to respond to this therapy, and hence might be classified as scurvy, the great majority of patients with the typical syndrome of thrombocytopenic purpura receive no benefit from its use even in massive doses.⁴ Hemophilia likewise is not helped in our experience.⁴

It has been possible to establish according to various workers that in many diseases with infection, with or without fever, a marked deficit of vitamin C does occur. Such is especially the case in pneumonia,^{22, 23, 24, 25} tuberculosis,^{26, 27} rheumatic fever and rheumatoid arthritis,^{28, 29, 30} whooping cough,³¹ and osteomyelitis.³² This should not be construed as proving an etiological relationship in these conditions or as establishing any curative value for the use of cevitic acid in such cases. It is, however, logical to attempt to replace this deficit, bringing the vitamin C content of the tissues up to normal as a matter of supportive therapy. Although encouraging therapeutic results have been reported in the treatment of intestinal tuberculosis,³³ whooping cough,³¹ and diphtheria^{34, 35} (especially combined with antitoxin), the preliminary paper by Gander and Niederberger²⁵ of Switzerland reporting their results following the use of massive doses in pneumonia is the most startling and hence in the greatest need of rechecking by other workers. By overcoming the total deficit (1000 to 2000 mg), usually present in pneumonia cases, in the first 24 hours they reported striking drops in the temperature curves similar to those obtained by serum therapy while the signs persisted for several days, as is also often seen following serum therapy.

Animal experimental studies have suggested that vitamin C might be of aid in the prevention and treatment of poliomyelitis^{36, 37, 38} and in the

encouragement of wound healing^{39, 40} but conclusive proof of its value in the clinical handling of these conditions is as yet not available

As a preventative against the development of secondary prescorbutic or scorbutic conditions we must in all diseases be careful to include an adequate supply of vitamin C in the diet. This is especially important where the intake is usually low as in diseases of the gastrointestinal tract and where the utilization is high, as in fever. When fruit juices are contraindicated cevitic acid should be given and when not well utilized by the oral route it should be given intravenously or intramuscularly.⁴¹

Evidence has been slowly accumulating which leads us to believe that there may be ingredients in citrus fruit and in other food substances which may play a part in helping to control certain types of hemorrhage but which are absent in the synthetic preparations of cevitic acid. Occasional cases have been noted by various workers, including ourselves, which do not respond to synthetic vitamin C but which respond to lemon juice or to an equivalent natural source.

In addition two other substances which may be termed vitamins (at least until more complete studies have been carried out) have been described by Dam⁴² and his coworkers and Rusznyak and Szent-Gyorgyi.⁴³ These substances, both of which appear to have antihemorrhagic properties, have been termed vitamins K and P respectively. Butt, Snell and Osterberg⁴⁴ have reported encouraging results from the use of vitamin K together with bile or bile salts in the treatment of jaundice very recently, but all of the work with these substances is in a very preliminary state and it cannot be considered that they are of established value at present.

DOSAGE

The curative and maintenance dosage of cevitic acid is in most instances between 30 to 50 mg per day orally. This varies greatly, however, and we have had patients in whom 1000 mg daily given by mouth failed to cure the scorbutic condition. This must have been due to faulty absorption from the gastrointestinal tract since intravenous administration produced rapid cure. Schultzer⁴⁵ produced evidence that at least in a small group of patients the results were as rapid using a dose of 40 mg as when 600 mg daily orally were given. We have had patients in whom less than 1000 mg doses intravenously failed to prevent the recurrence of scurvy. In some instances we have been so far unable to fully explain this experience.

Fortunately the toxicity of this substance is low so that overdosage does not appear to be harmful. Experimentally we have given as high as 10,000 mg intravenously in a single dose to one man and have given 1000 mg daily for many months intravenously without untoward effects, the excess beyond saturation being excreted.

The dosage for clinical use may range, therefore, between 30 mg orally, or intravenously, and up to 100 mg intramuscularly without danger

COMMENTS

It should never be forgotten that scurvy is a common disease, a common complication, easily missed, easily diagnosed and easily cured.

Our present knowledge leads us to conclude that the indications for use of cevitamic acid in medicine are dependent on the demonstration of a deficit or the danger of a deficit of this material in the body, whatever be the cause or the disease involved.

The use of tests for the vitamin C content of the blood, saturation with urinary determinations, and the capillary fragility tests will give a fairly complete picture of the state of vitamin C metabolism for study.

In the absence of facilities for chemical studies cevitamic acid may be administered safely on the basis of the suggestions outlined in this paper.

REFERENCES

- 1 ELMBY, A, and WARBURG, E Inadequacy of synthetic ascorbic acid as an anti-scorbutic agent, *Lancet*, 1937, ii, 1363-1365
- 2 WRIGHT, I S Treatment of adult scurvy with crystalline vitamin C, *Proc Soc Exper Biol and Med*, 1934, xxxii, 32
- 3 SCHULTZER, P Studies on capillary resistance, *Acta Med Scand*, 1934, lxxvi, 1-10; lxxxiii, 544-554, 1935, lxxxv, 563-573
- 4 WRIGHT, I S, and LILIENTELD, A Pharmacological and therapeutic properties of crystalline vitamin C, *Arch Int Med*, 1936, vii, 241-274
- 5 DALLDORF, G, and RUSSELL, J Effect of cevitamic acid injections on capillary resistance, *Jr Am Med Assoc*, 1935, civ, 1701-1702
- 6 FARMER, C J, and ABT, A F Ascorbic acid content of the blood, *Proc Soc Exper Biol and Med*, 1935, xxxii, 1625-1629
- 7 PIJOAN, M, and KLEMPERER, F J Determination of blood ascorbic acid, *Jr Clin Invest*, 1937, vi, 443-447
- 8 WRIGHT, I S, and MACLENATHEN, E Vitamin C saturation—kidney retention test, intravenous test dose of ascorbic acid, *Proc Soc Exper Biol and Med*, 1938, lxxviii, 55-59
- 9 WRIGHT, I S Present status of the clinical use of cevitamic acid, *Am Jr Med Sci*, 1936, cxci, 719-735
- 10 FLEMING, G W T H, and BURROWS, T E Possible discrepancy in the estimation of ascorbic acid in urine, *Brit Med Jr*, 1938, i, 333-335
- 11 HARRIS, L J, and RAY, S N Diagnosis of vitamin C subnutrition by urine analysis, *Lancet*, 1935, i, 71-77
- 12 JOHNSON, S W, and LIBVA, S S Urinary excretion of ascorbic and dehydroascorbic acids in man, *Biochem Jr*, 1934, xxviii, 1393-1408
- 13 ABBASY, M A, HARRIS, L J, RAY, S N, and MAROROCK, J R Diagnosis of vitamin C subnutrition by urine analysis, *Lancet*, 1935, ii, 1399-1405
- 14 YOUNG, J B, CORLETTE, M B, AKEROYD, J H, and FRANK, H Studies of vitamin C metabolism and saturation, *Am Jr Med Sci*, 1936, cxci, 319-333

- 15 WRIGHT, I S, LILIENFELD, A, and MACLENATHEN, E Determination of vitamin C saturation—a five hour test, *Arch Int Med*, 1937, **1**, 264-271
- 16 VAN ECKELEN, M Over Opname, Verbrink en Witscheiding von Vitamine C, Door de Mens, Utrecht, Drukkerij Fa Schotanus and Jens, 1936
- 17a DANIELS, A L, and EVERSON, G J Influence of acetyl-salicylic acid on urinary excretion of vitamin C, *Proc Soc Exper Biol and Med*, 1936, **XXXV**, 20-24
- b YOUMANS, J B, CORIETTE, M B, FRANK, H, and CORLETTE, M Failure of acetyl-salicylic acid to effect urinary excretion of vitamin C, *Proc Soc Exper Biol and Med*, 1937, **XXXVI**, 73-76
- 18 GANNON, C, and MCGOVERN, T Pyridium as a source of interference in vitamin C determinations, *Proc Soc Exper Biol and Med*, 1938, **XXXVIII**, 267-270
- 19 ROTTER, H Determination of vitamin C in the living organism, *Nature*, **CXXXIX**, 717
- 20 PORTNEY, B, and WILKINSON, J Intradermal test for vitamin C deficiency, *Brit Med Jr*, 1938, **1**, 328-329
- 21 GOTHLIN, G F Method of establishing vitamin C standard by testing the strength of cutaneous capillaries, *Skand Arch f Physiol*, 1931, **1**, 225-268
- 22 SCHROEDER, H Excretion in health and disease, *Klin Wchnschr*, 1935, 484-486
- 23 GULDAGER, A, and POULSEN, J E Undersgelser over c vitaminudskellelsen, *Hospitals-Tidende*, 1935, **lxxviii**, 1029-1042
- 24 HARDE, E, ROTHSTEIN, J A, and RATISH, H D Urinary excretion of vitamin C in pneumonia, *Proc Soc Exper Biol and Med*, 1935, **XXXII**, 1088-1090
- 25 GANDER, J, and NIEDERBERGER, W Vitamin C in the treatment of pneumonia, *Munchen med Wchnschr*, 1936, **lxxxiii**, 2074-2077
- 26 ABBASY, M A, HARRIS, L J, and ELLMAN, P Vitamin C and infection, *Lancet*, 1937, **1**, 181-186
- 27 HEISE, F H, and MARTIN, G J Ascorbic acid metabolism in tuberculosis, *Proc Soc Exper Biol and Med*, 1936, **XXXIV**, 642-644
- 28 ABBASY, M A, GRAYHILL, N, and HARRIS, L J Vitamin C and juvenile rheumatism, *Lancet*, 1936, **ii**, 1413-1417
- 29 RINEHART, J F Studies relating vitamin C deficiency to rheumatic fever and rheumatoid arthritis, *ANN INT MED*, 1935, **ix**, 671-689
- 30 RINEHART, J F, GREENBERG, L D, and BAKER, F Reduced ascorbic acid content of blood plasma in rheumatoid arthritis, *Proc Soc Exper Biol and Med*, 1936, **XXXV**, 347-350
- 31 ORNEROD, M J, and VONKAUF, B M Further reports on ascorbic acid treatment of whooping cough, *Canadian Med Assoc Jr*, 1937, **XXXVII**, 268-272
- 32 ABBASY, M A, HARRIS, L J, and GRAYHILL, N Vitamin C and infection, *Lancet*, 1937, **1**, 177-181
- 33 STEINBACH, M M, KLEIN, S J, and HIRST, A Personal Communication
- 34 MOMUSEN, H Remarks given before the Medical Society, Frankfort, *Munchen med Wchnschr*, 1935, **lxxxii**, 82
- 35 MESSER, H Beitrag fur Nebennierenrindentherapie bei Diphtherie, *Deutsch med Wchnschr*, 1936, **lxii**, 1131-1132
- 36 JUNGBLUT, C W Inactivation of poliomyelitis virus in vitro by crystalline vitamin C, *Jr Exper Med*, 1935, **lxii**, 517-521
- 37 JUNGBLUT, C W Attempts at vitamin C therapy in experimental poliomyelitis, *Jr Bact*, 1936, **lxvi**, 34-35
- 38 JUNGBLUT, C W Vitamin C in therapy and in prophylaxis in experimental poliomyelitis, *Jr Exper Med*, 1937, **lxv**, 127-146
- 39 JENEY, A V, and KORPASEY, V V Verzogerte Heilung der Haut- und Knochenwunden bei Skorbuttieren, *Zentralbl f Chirurg*, 1934, **1**, 2836-2846
- 40 WOLBACK, S B Source of intracellular substance in recovery from experimental scorbutus, *Am Jr Path*, 1933, **1**, 689-700

- 41 LILIENTFELD, A, WRIGHT, I S, and MACLENATHEN, E Intramuscular injection of ascorbic acid and excretion in the sweat, Proc Soc Exper Biol and Med, 1936, xxv, 184-189
- 42 DAM, H A new deficiency disease, Nature, 1934, cxxxiii, 909-910 A new deficiency disease in chicks, resembling scurvy, Biochem Jr, 1934, xxviii, 1355-1359 The anti-haemorrhagic vitamin of the chick, Biochem Jr, 1935, xlix, 1273-1285, and Nature, 1935, cxv, 652-653
- 43 RUSZNYAK, St, and SZENT-GYORGYI Vitamin P-flavenols as vitamins, Nature, 1936, cxxxviii, 27
- 44 BUTT, H R, SNELL, A M, and OSTERBERG, D Use of vitamin K and bile in treatment of haemorrhagic diathesis in cases of jaundice, Proc Staff Meet Mayo Clin, 1938, 72-78
- 45 SCHULTZER, P Saturation with ascorbic acid, Biochem Jr, 1937, xli, 1934-1938

CLINICAL AND HEMATOLOGICAL REVIEW OF SPRUE BASED ON THE STUDY OF 150 CASES

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MANSON described sprue as "an insidious chronic remitting catarrhal inflammation of the alimentary canal occurring particularly in Europeans who are residing or have resided in tropical or subtropical climates" Certain investigators, such as Newham, Morris and Manson-Bahr¹ stress the fact that the anemia of sprue is secondary to a gastrointestinal lesion and not due to disease of the blood-forming organs The disease, however, is classified in some of the standard textbooks under Diseases of the Hematopoietic System and in others it is included under Gastro-Enterology Now, is sprue primarily a disease of the alimentary canal or a blood dyscrasia?

By presenting the data gathered during a study of 150 cases we shall endeavor especially to clarify this fundamental issue No attempt will be made to discuss all aspects of the disease

ANALYSIS OF THE SERIES

The present series is made up of 150 persons all but two of whom are natives of Puerto Rico There were 121 whites, 26 mulattoes, and only 3 negroes The ages ranged from 9 to 84 years One-third of the patients were less than 40 years old, a point of difference from true Addisonian anemia

In general appearance certain of our older patients presented strong resemblances to persons with pernicious anemia Loss of subcutaneous fat, and wrinkling and pigmentation of the skin, especially on the arms and legs, favor the diagnosis of sprue In contrast to pernicious anemia the spleen was always normal or small Although purpuric or scorbutic spots were occasionally found, retinal hemorrhages were uniformly absent

Students of non-tropical sprue, such as Hansen and Staa,² have emphasized the occurrence of tetany, osteoporosis and osteomalacia Our tropical experience has included occasional instances in which there were decalcified areas in the costal cartilages We have never found osteoporosis, osteomalacia or tetany

ETIOLOGY

Our studies do not support the opinion that sprue is contagious We did find, however, that in 75 per cent of the cases in which a reliable history could be obtained sprue or pernicious anemia had existed in one of the patient's parents, usually the mother We therefore believe that a hereditary factor is present

* Delivered before the American College of Physicians, New York City, April 7, 1938

Of the many theories of the etiology of sprue only the concept of a deficiency disease has been able to withstand prolonged investigation. Castle, Rhoads and their collaborators³ while working in Puerto Rico confirmed the belief that deficient diets frequently antedate the onset of clinical sprue. They demonstrated that feeding of the vitamin B complex, in the form of autolyzed yeast, produces reticulocyte crises and improvement of the blood picture in certain cases. The intrinsic gastric factor was found lacking in other instances and some of the more severe or advanced cases showed an apparent defect in absorption from the intestinal canal. Castle states "it is probable that the usual type of diet is such as to favor a diminished consumption of some of the known sources of the extrinsic factor, such as meat, eggs and whole grain cereal." Recent unpublished analyses by the Chemistry Department of the School of Tropical Medicine* definitely established that the Puerto Rican diet is inadequate in vitamin A, low in calcium and phosphorus, low in fat and high in carbohydrates. The protein is sufficient quantitatively but is poor in quality. The amount of iron was found to be higher than in the normal continental diet.

A comparison between the average continental diet (2400 calories) and that of the Puerto Rican peasant or "jibaro" follows:

	Continental	Puerto Rican
Vitamin A	7895 Units	1220 Units
Calcium	0.35 Gm per 100	0.29 Gm per 100
Phosphorus	1.25 Gm per 100	0.73 Gm per 100
Proteins	55 Gm	58 Gm
Fats	98.97 Gm	61.70 Gm
Carbohydrates	321.33 Gm	400.54 Gm
Iron	0.021 Gm per 100	0.032 Gm per 100

This most inadequate diet has been taken steadily since childhood by many of the sprue patients, true enough, but it has also been taken by nearly all those suffering from hookworm infestation. Yet both clinically and hematologically the hookworm anemia differs from that of sprue. The former is invariably hypochromic, microcytic or normocytic, the latter is typically macrocytic. Diet therefore is far from explaining the whole story.

CIRCULATORY SYSTEM

It is well known that deficiency of vitamin B may affect the heart. Since the Puerto Rican diet is probably deficient in vitamin B and since the administration of vitamin B has been beneficial in sprue, special studies were made of the circulatory system in our patients. Twenty-five untreated patients were selected at random from the group. The venous pressure and circulation time were normal. The cardiothoracic ratio averaged 44 per cent, and in only one instance exceeded 50 per cent. The vast majority of the patients had a vital capacity from 200 c.c. to 1200 c.c. below normal. In our series the blood pressure was low. It should be mentioned, however,

* Personal communication of Dr. J. A. Mayer

that a general response to treatment has usually been accompanied by a gradual rise of pressure. In a few cases definite hypertension and left ventricular preponderance appeared.

METABOLISM AND DIGESTION

Studies of gastric secretion revealed almost universal hypochlorhydria or achlorhydria, despite the injection of histamine.

Investigations of glucose tolerance proved especially fruitful. Virtually all our patients had low fasting blood sugar values. The ingestion of 75 gm of glucose usually did not raise the glucose level by more than 15 mg per cent. In most of the younger patients the glucose curves returned to normal as the disease yielded to treatment. This agrees with the findings of Thaysen. Five of our older patients, however, retained flat glucose curves after complete recession of the clinical and hematologic abnormalities and despite continued injections of liver extract. This seems to show that the gastrointestinal tract may remain permanently damaged in occasional cases.

As already observed by Hanes⁴ our blood sugar curves were high when glucose was administered intravenously. This fact, together with the observations of Barker and Rhoads,⁵ favors the theory of deficient intestinal absorption and tends to make the hypothesis of pancreatic disease less important in our understanding of sprue. The pancreas was found to be normal in 18 of 20 cases studied at autopsy.

The late lamented Thaysen⁶ of Copenhagen declared that celiac disease, non-tropical sprue, and tropical sprue are one disease. He set forth the following features as characteristic: (1) Abnormal excretion of fat in the feces, (2) normal or slightly increased fecal nitrogen, (3) flat blood-sugar curve, (4) increased basal metabolism. He stated that these four metabolic disturbances were conjoined in no other disease. He regarded their presence as proof that the aforementioned diseases are identical.

We grant that steatorrhea and flat glucose curves occur regularly in tropical sprue. Nitrogen determinations have not been made. Studies of the remaining criterion—namely, basal metabolism—do not support Thaysen's contention, but show instead a low level of metabolism. In 10 typical cases selected at random the readings ranged from plus 4 per cent to minus 23 per cent.

BLOOD AND BONE MARROW

The blood was studied by the methods of Wintrobe. With the exception of one atypical case the lowest mean cell volume in the series of 150 cases was 102 cubic microns, the highest was 220 cubic microns, and the average for the series was 123.6. The color index was below one in 23 cases. The highest index was 2.2, the average was 1.22. The volume index was never below 1.0, the maximum was 2.3, the average was 1.39.

The mean cell hemoglobin varied between 26 and 59 micrograms, with an average of 36.6. The mean cell hemoglobin concentration was found at 22 per cent or lower in four cases, the lowest figure being 20 per cent. The highest was 45 per cent, the average was 26.1 per cent.

The hemoglobin averaged 66 per cent. The erythrocytes ranged from 690,000 to 4,410,000 per cubic mm, with an average of 2,710,000. Leukocytes ranged from 1,550 to 13,600, the average being 5,280.

Thus the anemia was found to be macrocytic, usually hyperchromic, occasionally hypochromic, very rarely normocytic, never microcytic.

With the possible exception of one case reported by us⁷ (*Revista Medica de Barcelona*), in all cases of a microcytic hypochromic anemia the diagnosis of sprue has failed the test of thorough clinical and anatomical investigation.

Our studies of the sternal marrow yielded new and significant data. Observations were made by the aspiration method of Osgood and Young in 40 cases. Of these we shall use only 28 in which material was obtained before treatment and again 10 days and 2 months after the first injection of liver extract. Differential counts were made from smears of aspirated marrow stained with Jenner-Giemsa, 500 cells were counted in each smear.

Megaloblasts were frequently seen. Usually there were more erythroblasts late or early than normoblasts, but only in five cases did megaloblasts outnumber the normoblasts. Megakaryocytes, plasma cells and monocytes were very rarely seen. The lowest megaloblast count was 0.2 per cent, in a case showing very few erythroblasts and a relatively high proportion of normoblasts. The highest figure for megaloblasts was 23.4 per cent. This case showed 12.2 per cent early erythroblasts, 9.8 per cent late erythroblasts, and 8.6 per cent normoblasts.

The following table (table 1) portrays the average differential counts of the aspirated marrow in 28 cases. It will be observed that the megaloblasts

TABLE I
Sprue

Sternal Marrow (500 cells counted)	Initial	10 Days	2 Months
Megaloblasts	6.31	1.79	0.60
Erythroblasts (Early)	8.71	3.06	1.17
Erythroblasts (Late)	11.12	5.23	2.80
Normoblasts	15.59	11.68	11.26
Myeloblasts	.72	1.24	0.63
Pro-myelocytes	2.60	3.53	3.40
Myelocytes (Neut.)	17.83	16.46	17.51
Myelocytes (Eos.)	2.77	3.54	2.51
Myelocytes (Baso.)	0.30	1.78	0.40
Polynuclears (Neut.)	26.92	44.14	51.91
Polynuclears (Eos.)	1.91	1.26	2.43
Monocytes	0.03	0	0
Lymphocytes	5.11	5.95	4.89
Megakaryocytes	0.07	0.24	0.06

blasts gradually declined to the low level of 0.6 per cent after two months of treatment, while the neutrophilic granulocytes rose from 26.92 per cent to 44.14 per cent in 10 days, reaching 51.91 per cent at the end of two months. The erythroblastic elements decreased from 41.73 per cent to 15.83 per cent in two months. At the same time the myeloblastic element rose from 53.05 per cent to 78.79 per cent.

In three cases we were able to observe marked hematologic changes in the marrow three days following the first injection of liver extract, before any signs of regeneration could be detected in the peripheral blood and before any improvement had occurred in the symptoms. In one of these three cases (table 2) a rapid maturation of megaloblasts was taking place. Within three days the proportion of megaloblasts fell from 23.4 per cent to 12.2 per cent. Early erythroblasts fell from 12.2 per cent to 8.8 per cent. Late erythroblasts rose from 9.8 per cent to 23.2 per cent and normoblasts rose from 8.6 per cent to 28.8 per cent.

TABLE II

Sternal Marrow (500 cells counted)	Initial	Third Day
Megaloblasts	23.4	12.2
Erythroblasts (Early)	12.2	8.8
Erythroblasts (Late)	9.8	23.2
Normoblasts	8.6	28.8
Myeloblasts	6	0
Pro-myelocytes	2.0	6
Myelocytes (Neut.)	12.4	7.6
Myelocytes (Eos.)	2.2	2.0
Myelocytes (Baso.)	2	0
Polynuclears (Neut.)	18.2	13.8
Polynuclears (Eos.)	2.8	2.0
Monocytes	4	0
Lymphocytes	7.0	1.0
Megakaryocytes	2	0

IS SPRUE PRIMARILY A DISEASE OF THE GASTROINTESTINAL TRACT?

The prominence of the gastrointestinal manifestations in sprue and the recurrence of cramps and diarrhea in some cases after complete hematological improvement has taken place are circumstances which have led to the belief that the disease is primary in the gastrointestinal tract. On the other hand it is our impression that patients suffering from anemia rarely apply for treatment until the disease is far advanced. In contrast with this, patients who have diarrhea are more apt to apply for early medical attention.

We have had occasion to study very early cases of sprue—cases of one to two weeks' duration. Examination invariably showed the presence of macrocytic anemia and of megaloblastic bone marrow. Still more convincing are the cases which have shown only a macrocytic anemia for weeks and months prior to the appearance of the typical glossitis and digestive disturbances.

Additional evidence lies in the fact, previously mentioned, that after liver therapy maturation of the megaloblasts in the marrow occurs before the digestive disturbances begin to improve

TREATMENT

Unquestionably the two most important factors in the treatment of sprue are an appropriate diet and adequate liver therapy. Ashford insisted on the necessity of a high-protein, low fat and low carbohydrate diet, and his opinion has been confirmed by almost all the physicians of Puerto Rico. Miller and Barker⁸ state that "The maintenance of a diet for sprue in addition to liver therapy gives a patient more complete relief from gastrointestinal symptoms than does liver extract alone."

In the older patients, in whom more or less permanent gastrointestinal degeneration has occurred, liver extract even in large doses has usually failed to abolish the diarrhea unless a strict dietary regimen is followed.

In previous communications^{9, 10} we have reported the therapeutic failure in sprue of certain preparations which had been considered potent in the treatment of Addisonian anemia. Ventriculin, Extralin, and Autolyzed Liver Extract have failed in sprue. The failure cannot be attributed entirely to deficient absorption, for in some cases aqueous liver extract (Valentine) has been successful. The highest reticulocytosis observed in sprue (65 per cent) occurred in a patient who received aqueous liver extract "per os" after full doses of Ventriculin during 15 days had shown no effect.

Lilly's number 343 (Castle's formula) is a relatively crude or diluted extract, high in ash. It contains much inert material and probably carries with it an appreciable amount of what we might call the B₂ complex. Without doubt it is highly effective in the treatment of sprue anemia. Lack of response of this anemia to a concentrated extract as contrasted with positive response to the cruder extract, if demonstrated, would therefore serve to differentiate sprue from Addisonian pernicious anemia and to establish B₂ hypovitaminosis as the most important factor in the etiology of sprue.

This idea was tested in 70 cases. Five patients received a single 2 c c dose of Lederle's concentrated extract intrasternally. The resultant reticulocytosis averaged over 20 per cent, and the glossitis rapidly disappeared. The other 65 patients received intramuscular injections of 1 c c daily for three days, then every third day for one month, then every five days for one month, a dose larger than that recommended for pernicious anemia. Sprue is more resistant than pernicious anemia and requires larger doses of liver. The highest reticulocyte response occurred in the most anemic patients.

We obtained a higher reticulocyte response using diluted extracts in the group of patients having initial red cell values of less than a million. In all other groups the response to the concentrated extract compares favorably with that produced by other crude extracts and also with the American Medical Association's standards of potency in pernicious anemia.

Thus, liver concentrate is highly effective in all cases of sprue characterized by macrocytic anemia, whether hyperchromic or hypochromic

Four patients in the present series of 150 showed definite evidence of spinal cord involvement. In each case the neural symptoms improved under treatment.

In Puerto Rico the death rate from sprue is 65 per million inhabitants. This rate has not changed in recent years.

CONCLUSIONS

- 1 A clinical and hematological survey of 150 cases is presented.
- 2 It is evident from this survey that there is a definite racial predisposition and a probable hereditary factor in sprue.
- 3 Bony changes, reported by European and continental American investigators of sprue, were not found in this series.
- 4 The basal metabolism, studied in 10 cases, was found to be low.
- 5 Since Puerto Rico is a tropical island in which diarrheal diseases are prevalent the glucose tolerance test must be used for prognosis rather than diagnosis in Puerto Rican cases of sprue.
- 6 The most constant laboratory finding is macrocytic anemia usually hyperchromic, occasionally hypochromic, with a megaloblastic type of marrow.
- 7 We are inclined to regard sprue as primarily a disease of the hematopoietic system, not of the gastrointestinal tract.
- 8 Despite its low vitamin B content, concentrated liver extract was found to be highly beneficial in the treatment of sprue, including cases with spinal involvement.
- 9 The death rate from sprue in Puerto Rico is estimated as 65 per million inhabitants per year.

BIBLIOGRAPHY

- 1 MANSON, B. *Manson's tropical diseases*, 1936, William Wood and Co.
- 2 HANSEN, K., and STAA, V. H. *Die Einheimische Sprue und Ihre Folgekrankheiten*, 1936, George Thieme.
- 3 CASTLE, W. B., RHOADS, C. P., LAWSON, H. A., and PAYNE, G. C. Etiology and treatment of sprue, *Arch Int Med*, 1933, lvi, 627.
- 4 HANES, F. M., and MCBRYDE, A. Identity of sprue, non-tropical sprue and celiac disease, *Arch Int Med*, 1936, lvi, 1.
- 5 BARKER, W. H., and RHOADS, C. P. The effect of liver extract on the absorption of fat in sprue, *Am Jr Med Sci*, 1937, cxiv, 804.
- 6 HESS THAYSEN, E. *Quart Jr Med*, 1935, iv, 359.
- 7 SUAREZ, R. M. Anemia perniciosa de tipo macrocitico, *Rev Medica de Barcelona*, 1934.
- 8 MILLER, D. K., and BARKER, W. H. Clinical course and treatment of sprue, *Arch Int Med*, 1937, lx, 385-566.
- 9 SUAREZ, R. M. Hematological studies in sprue, *Bol Asoc Medica de Puerto Rico*, 1935, xxvii, 239.
- 10 SUAREZ, R. M. El Tratamiento del Espru y el uso del Extracto Acuoso de Hígado on su Anemia, *Bol Asoc Med de P. R.*, 1936, xxviii, 74-86.

THE SOCIAL RESPONSIBILITIES OF MEDICINE

By JOHN P. PETERS, *New Haven, Connecticut*

THE social responsibility of medicine, as I see it, is to provide to all classes of the population medical care of the highest quality. A lesser adjective like adequate is so indefinite that it can be argued out of all meaning. It is hardly necessary to say that any program that professes to provide the highest quality of medical care must include measures for its continuous improvement.

This premise may be challenged on the grounds that members of the medical profession have no greater moral responsibility to the public than do men and women in other walks of life, that medicine can not be reorganized apart from the rest of the social structure, and that, in any event, it will advance best under the laissez faire principles of free competition. Granted that all professions or trades have an equal responsibility, there is no reason why medicine should not lead the others in the discharge of duty. As to laissez-faire principles of free competition, they are abhorrent to the traditions of medicine with which we its priests have taken such care to inculcate the multitude. In its baldest terms this tradition holds that medicine is not a mere commodity to be sold competitively at the highest price and that its dispensers are not simply salesmen free to employ all the advertising tricks of the hawkster. We employ the bedside manner, not the sales manner, our personal relations are all sacred, not carnal, our art of medicine is a supplement, not a substitute, for science. Medicine can not have its cake and eat it. If it insists on its unique altruism and solicitude for the public weal, the public will take it at its word. I may seem just now to have ridiculed some of the concepts that many of you cherish. It is not the concepts, but the clichés in which they are expressed and certain implications of these clichés that drive me to ridicule. During the last few months my attention has been much directed to certain defenses of the present system of medical practice. The most recurrent arguments are declarations of good-will and the satisfactory state of existing conditions, assertions that those who labor in the making and teaching of medicine know nothing of its application, and claims that all incentive to labor and all the human amenities will vanish if an individualistic relation between patient and physician, involving personal payment in the coin of the realm, is abolished. At this point I must confess some prejudice. Confronted with the dictum that the scientific investigation of medicine is incompatible with its clinical application I am at a loss whether to forsake laboratory or clinic. When, in addition, I learn that the full time man has no incentive for work and can not establish with patients the personal relations that are essential to the proper conduct of medical practice, I am constrained to drop both. Fortunately

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at this juncture I am reminded that the realistic humanity of the salaried trained social worker is infinitely more effective in the diagnosis and treatment of social ills than the conditioned sentimentality of the high-minded ladies I remember in my father's parish

The most distinctive feature of our era is the enormous technological advances that have come from the rapid development and exploitation of scientific discoveries. One of the inevitable consequences of this has been the substitution for individualistic enterprise of large organizations which can assemble and coordinate the skills and facilities necessary for production under the new system. Medicine as a whole has evaded this movement, in spite of the fact that it has been greatly affected by technological advances. Modern methods of diagnosis and treatment require a breadth of knowledge, a mastery of technic and material equipment that no one man can hope to possess. And if he did possess them he could not profitably exploit them by his own undivided efforts. In addition science is marching with an ever accelerated tempo that makes it impossible for a single individual to keep abreast of its advances in the whole field of medicine. In the face of these facts it is mawkishly sentimental to bemoan the loss of the physician who practised all branches of the healing art.

It is absurd to argue that, because most ailments are trivial and can be treated without special skill or equipment, experts with modern facilities need be available only for exceptional cases. It is the detection of these exceptional cases that demands the highest powers of discrimination. The increasing complexities of medicine have led its practitioners more and more to specialize. Since there is no other means of securing expert service this tendency to specialization cannot and should not be checked. However, although almost any technical procedure can be mastered by persons with moderate intelligence and average dexterity, something more than these attributes is needed to guarantee the intelligent application of this technical skill. Society must be assured that technical proficiency is not exercised for its own sake, but only under the control of responsible judgment. In other pursuits, confronted with the same problem, a solution has been found in organization. Some similar coordination of medical services would seem to be desirable, if not inevitable. Group practice, a device for securing such coordination in an individualistic system, is unfortunately more certain to achieve economy and profits than high quality of service. Moreover, its benefits must be largely confined to the self-supporting class.

To provide the highest quality of medical care for every person, modern facilities for diagnosis and treatment, in the hands of capable personnel, under competent direction, must be universally available. The cost of such a program under the present system would have to be borne by the patients as individuals. It is self-evident that none of these costs can be met by the poorest members of the population. This class which can not pay for its medical care is larger than the class which for general purposes is termed indigent. Medical costs are occasional, not continuous like the

prime necessities, food, clothing and shelter, they may vary from nothing to an indefinite amount and cannot, therefore, be budgeted with accuracy. In addition the disabilities of illness impose a double burden—the cost of medical care proper and the loss of earning power. In illness increased costs coincide almost invariably with diminished income, the otherwise self-supporting individual may at any time be reduced by illness to the indigent class. It is forever to the honor of the medical profession that its members have uniquely recognized their responsibility to serve gratuitously those who can not afford to pay. It is, however, fundamentally inequitable for society to accept these services without remuneration, and it is economically impracticable for physicians to offer them. Proper care consists no longer of purely personal services, it involves the purchase and maintenance of expensive equipment. If the physician is to provide these facilities free to some patients, he must be remunerated by others. The ultimate burden of his charity falls only partly on himself, partly on his more wealthy patients, who therefore pay an extra penalty for illness. Furthermore, unless these supercharges are sufficiently large the highest quality of service can not be maintained. The burden of caring for the indigent must be distributed so that it falls equitably upon the whole population. I believe this is possible only if it is transferred to the government. Philanthropy, even if it takes the form of community chests, is too casual and penalizes virtue and generosity. If, however, the community is to assume the burden of caring for the indigent, it has the right to demand that the medical care it subsidizes be both economically and efficiently administered. Personnel must be carefully selected, responsibility and duties properly allocated, and equipment and facilities centralized to obviate unnecessary duplication of effort and materials.

Above the medically indigent is a larger group, probably the largest in the population, which can pay something for medical care. The number who can actually assume the total costs depends entirely upon the standards which are set. This number can be increased if either the incidence and duration of disability or the costs incurred through this disability are met collectively. This is the argument for medical cooperatives and contributory health insurance. With the general trend towards social security legislation, I personally believe that some form of health insurance is likely to be imposed upon us. If we are to have unemployment insurance there is no reason why unemployment through illness should not be compensated just as much as unemployment arising from faults in the economic structure. For the relief of this purely economic aspect of ill health, insurance may be a necessary and beneficial social expedient in which the interest of the physicians is no greater than that of any other body of citizens. When, in addition, insurance includes the provision of medical services, the interests of the medical profession are directly touched. In those countries in which compulsory health insurance has been introduced it has vindicated itself inasmuch as it has insured wider distribution of existing medical

services to the class to which it applies with more certain compensation to physicians who practice under its provisions. Nevertheless it is not a panacea for the ills of the medical system. Contributory insurance, especially when it is confined to that class which is on the precarious margin of economic competence, can not provide medical care of the highest quality nor does it promise anything for improvement of quality. It offers nothing to the truly indigent and is entirely inapplicable to thinly populated areas.

I have dwelt particularly on health insurance, not because of its intrinsic importance to my theme, but because it illustrates a general error that vitiates the formulae that have been proposed for the solution of the problem of popular health. Whether these emanate from lay or medical sources all are apparently predicated on the assumption that the medical profession is built on the lines of the medieval guilds with physicians holding the position of the artisans of a previous era. Actually, however unpleasant it may sound, in this respect too, medicine has been transformed quite as relentlessly as have all activities that have their roots in science. The practitioner has fallen almost completely into the derivative position of distributor or dispenser. The productive services of medicine have been largely taken over by educational and research institutes and hospitals. No program for the improvement of medical care that considers only the distributors to the neglect of these productive services can be satisfactory. It is a little tiresome to hear from our professional publicists of medicine that only practitioners have any comprehension of the problems of medical care.

A first class medical training has now become more costly than any other kind of education. The students can bear only a small and diminishing proportion of the expenses. The high school education, which used to provide a satisfactory background, must now be supplemented by a carefully selected college course. This must be followed by four years of medical school and at least a year as intern in a hospital. Those who wish to perfect themselves in any particular branch of medicine must prolong this hospital residence, often for from three to six years. The financial return throughout this training seldom rises above the subsistence level, although during their hospital residence, at least, these men are performing useful services. Under this system educational opportunities largely depend upon economic self-sufficiency. Of those who do not belong to the fortunate leisure class it is too often the unambitious who linger in our hospitals and medical schools, preferring security on a pittance to the struggle of competition. The movement to pay interns, which is rapidly gaining strength, especially in public hospitals, has justice to recommend it. If it finally prevails, however, it will place an additional burden on institutions which are already in financial straits.

It is unnecessary to linger long upon the enormous physical plant which the modern medical school must possess and maintain. The faculty, which only a generation ago was composed of physicians who derived their income from practice, must now include members who have not even had a medical

education (physicists, chemists, biologists, etc.) and who are dependent entirely upon their educational salaries. The incomes of members of the clinical faculties of the best schools are coming increasingly from salaries instead of private practice, as medicine becomes more complex and the educational responsibilities more exacting. These changes have undoubtedly improved the quality of teaching, but the scale of remuneration is so low that only those who have an extraordinary interest in investigation and teaching can remain on the full time faculty. And these have too little opportunity for the pursuit of the activities which alone can compensate the economic and social sacrifices they have made. Medical teaching has few of the allurements of academic leisure because it includes, besides the usual educational duties, responsibility for the care of patients in an exemplary manner. Since these clinical functions constitute a public service, in most instances neither hospital nor medical school feels any obligation to finance them separately.

The chief laboratories of the clinical departments of a medical school are hospitals. Without them no school can possibly survive. The old days of apprenticeship in the offices of practitioners are gone. Because teaching hospitals are indispensable to universities, the communities in which these institutions are placed adopt a mendicant attitude. The services of the schools and hospitals are accepted like the manna from heaven, while funds to support them must be sought from Foundations and philanthropically minded individuals. Although most of these institutions receive some aid, directly or indirectly, from one or more branches of the government, this rarely, if ever, even repays them for the burden they assume in behalf of the government.

The plight of hospitals which neither receive government aid nor have educational connections is even more deplorable. Unless they can find some fairy godfather to support them in luxury their facilities must be allowed to deteriorate or some of their patients must be charged fantastic amounts in behalf of the others. Services of physicians to the indigent in these hospitals either in wards or out-patient departments, are almost invariably gratuitous. Despite the highest ideals of these physicians, these services must often be relegated to a position of secondary importance in the struggle for a livelihood. In addition to providing care for its own inmates the modern hospital usually offers to the physicians of the community diagnostic and therapeutic facilities. In theory these services are manned by a more or less expert staff. In actual fact, since hospitals can not afford to remunerate this staff generously nor offer it opportunities for personal development and original work, the personnel is not usually of the highest quality. The future for its members is either to supplement their salaries by increasing private exploitation of their special training or to sink to the position of high-class technicians.

The productive investigations which advance medical knowledge are conducted chiefly in the medical schools and hospitals of this country.

Special Research Institutes and Public Health Departments of the government contribute to the total. Owing again to limited time and equipment, the part played by the private practitioner in the scientific advance of medicine becomes steadily less important. Even the organized forces of medicine contribute little but publicity. Both physicians and the public are proud of the important place which our country has attained in medical science, both benefit by these scientific achievements, but both discharge their responsibility chiefly in boasts.

Here, as I see it, is the crux of the dilemma. The great majority of physicians in this country is engaged in the distribution of medicine, not in its production. The solutions they offer for problems of health are naturally devised from the distributor's point of view. They are not uninterested in education nor unaware of the need for expansion of hospitals and educational machinery, but their proposals for the improvement of medicine are limited chiefly to measures which will allow them to utilize the resources of medical schools and hospitals for the care of their patients. They clamor for post-graduate courses by which they may be kept abreast of medical advances, from schools that are hard pressed to meet their obligations to undergraduate medical students. They ask that they be allowed as individuals to exploit hospitals and the diagnostic and therapeutic facilities that these institutions offer. They even demand the right to dispense, without control, materials provided by the government public health services. They exploit scientific discoveries to which they have contributed nothing. The burden of providing and maintaining all these services falls directly neither on them nor their patients, but is divided between government and philanthropy.

On the other side stands the consumer complaining of the unsupportable costs of medicine and searching for means to meet the bills for doctors, nurses, drugs, and possibly maintenance in a hospital. His attention is also centered on the process of distribution, his interest lies in his own illnesses. His powers of discrimination are slight, his insight into the problems of health and medicine slighter. He knows only that he wants both of the highest grade at the lowest possible price. He must be taught with stern honesty what these desires entail, not placated with fairy stories about the happy state of the present system of medicine.

Evidently, if reorganization for the improvement of medical care is contemplated, production must be considered quite as much as distribution and consumption, because it is production that ultimately determines the quantity and quality of the supply. It is in their complete neglect of the productive aspects of medicine that such measures as health insurance and ordinary cooperative organizations fail to meet the situation. It is in the same respect that the untrammelled control of medicine by its distributors falls short. In every other walk of life part of the payment which the distributor receives from the consumer for services reverts to the producer. It would be unfortunate if medicine followed this general commercial prac-

tice But, if it does not, it must ultimately find an alternative, and the only sound alternative thus far discovered for the support of non-remunerative enterprises is governmental subsidy

It is my impression that the government alone can assume the burden of providing, maintaining and correlating the necessary medical resources Such a suggestion immediately arouses cries of bureaucracy, and corruption, as if these were inevitable attributes of our political system The medical profession should be the first to deny such allegations It is its proud boast that the public health services of this country have been free from corruption and politics But, in any case, there is no good reason to believe that government direction would be worse than the whims and vagaries of philanthropists or the publicists and promoters who have the disposition of large funded fortunes Nor are the subsidies from the manufacturers of proprietary foods, drugs and medical instruments likely to direct education, investigation and practice into the most desirable channels

It is my opinion, further, that costs must eventually be collected by general taxation Those who can pay for their own care and prefer to patronize physicians of their own choice should not escape the general tax on this account, because this will not be imposed merely to pay for personal services but for the productive work that makes those services valuable It is rather amusing to reflect that at the present time most of the advances in medicine which the rich enjoy are developed in hospitals and institutions through the instrumentality of indigent patients The fees which the rich pay, however, do not return to the support of these institutions or the patients in most instances, but go to the practitioner who is exploiting the new medical discoveries The discharge of his deeper medical debt should not be left to the caprice of the wealthy patient, because there is no assurance that his whim will be wisely directed It is much more likely to be dictated by emotions connected with his personal experiences than by the general medical interests of the public

Preconceptions and prejudices must be abandoned, whether they be political, economic, social or medical There are those who shudder at the thought of governmental control in any province of life, others to whom the word federal has a peculiarly vicious significance Yet all recognize that due participation of local, county, state and federal governments in the interests of the common weal is a necessary bulwark against anarchy All these branches of the government at present share the burden of public medical and health services, no one of them can or should be completely excluded The most pressing present problem of government is the discovery of the formula that will assure proper allocation of responsibility and expert control This is more likely to be attained, in my opinion, if the initiative is taken by those who are expertly trained In any reorganization of medicine this means primarily physicians In attacking the problem, the improvement of medical care, not costs nor remuneration, must be the prime

objective No one yet knows what the highest quality of medical care would cost nor what it might be worth

These are bold statements and are sure to arouse at once cries of socialism or worse I should hope this company would not be frightened by mere words Large ends can not be gained by little means and the goal I have set is highly ideal A sweeping program suddenly imposed on this country as a whole, out of the head of any Jove, would undoubtedly create confusion, if not chaos Thoughtful investigation and experiment promise more than grandiose projects born of emotional preconceptions The program must be built in an evolutionary manner, step by step, with thought to the resources and personnel now available and the need for developing more and better resources and personnel The investigation of the extent of medical indigence projected by the American Medical Association must be searching and not too limited in its scope But this should be only the first of a series of investigations which must measure the extent of our assets as well as our liabilities Experimentation in the solution of local and general problems of medical care must be encouraged, not suppressed Education and investigation must be supported and extended and opportunities for work in these fields must be multiplied and made more attractive, with every protection against inept control, regimentation and the destruction of initiative and imagination Until these investigations have been made anyone is arrogant indeed who claims that he has a program that will solve the problems of medicine in a "nation comprised of forty-eight states in which climatic, economic and social conditions vary greatly" But he who doggedly resists change either because of personal satisfaction with his present condition or because Utopia seems an idle dream, betrays both the art and the science of medicine Because both art and science know no limits and defy all restrictions

CASE REPORTS

GASTROSCOPIC OBSERVATIONS OF SYPHILIS OF THE STOMACH¹

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ENGLISH medical literature contains no gastroscopic description of syphilis of the stomach of the *linitis plastica* or leather bottle type. Schindler's¹ English text mentions cases seen with Moutier and referred to in the latter's French text, and in addition describes two syphilitic stomachs of contracted hour-glass type, both of which had been treated (one operated upon) and which showed only healed scars at time of gastroscopy. Renshaw,² in discussing the differential diagnosis of tumors of the stomach, refers to syphilis of the stomach as having "no constant characteristics." "There have been tumors with and without ulcers. The positive blood serum reaction is the only definite differential point." Kerkhof³ describes a case of a large ulcerous lesion thought to be luetic because of a positive Kahn reaction, but which was subjected to biopsy because of the suggestive appearance of malignancy. The biopsy showed definite perivascular infiltration and lymphocytes and plasma cells deep in the submucosa, and the suspicion of syphilis was confirmed. He noted gastroscopically subsequent healing to scar tissue after antiluetic treatment. Henning's⁴ English text does not mention syphilis of the stomach specifically. Swalm, Jackson and Morrison,⁵ in a report of different types of chronic gastritis, include one case marked "luetic etiology," but no clinical details or reports on serologic examination are given.

Gutzeit and Tertge⁶ show two pictures of syphilis of the stomach. One (*Bild 56*) is described as a red, speckled, rough mucosa with thick swollen folds in a male patient 56 years of age, with achylia and "latent lues." Another, a patient with *tabes dorsalis* (*Bild 71*) also shows a red-flecked mucosa with hypertrophic changes and swelling of folds. Both of these pictures resemble the appearance seen in our case after treatment. They further state that cases of lues with primary lesions and with skin eruption show nothing gastroscopically or only a mild superficial catarrh. The treated or healed syphilitic patients showed superficial catarrh with atrophic changes, sometimes atrophic gastritis, rarely hypertrophic gastritis, more often a swollen condition of the mucosa. In latent lues a smooth condition of the mucosa was seen, regardless of whether the patient had or had not received treatment, and in *tabes* a similar condition, with hypertonicity (or contracture?). Their conclusion is that the tendency in syphilis, where any change in gastric mucosa occurs, is toward an atrophic state.

Moutier has the most complete gastroscopic description of syphilis of the

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stomach. He divides the cases into those showing tumor (gumma) formation and leaving a localized scar on healing, ulcerative forms, single or multiple, also on healing leaving scars, with more contracture and distortion of the stomach (hour-glass), and those showing a generalized gastritis, often hemorrhagic, resulting in atresia (*limitis*) by submucosal involvement. The plates shown in his text (XII, 1 and 2, and XII, 3) illustrate the localized varieties.

The only cases of *limitis plastica* comparable to our own are described by Moutier⁷ (page 167).

The first is that of a 60-year old man, known to have been luetic for 25 years, with achylia but, at the time of observation, with a negative Wassermann. The roentgen-ray examination showed a small, contracted stomach transversely situated high under the diaphragm and liver, with a small air bubble and normal emptying time. Gastroscopy showed a very small gastric lumen, hardly distensible by inflation and extremely intolerant to air. Hypersecretion with adherent mucus on the walls was noted. During the examination there was very violent antral spasm. The pylorus was hardly visible, high and to the right (posteriorly placed). The folds were very large (thickened) in the antrum. There were several hemorrhagic areas on the lesser curvature. The mucosa of the body of the stomach appeared thick, but not hypertrophic.

Another case was of a 40-year old man, said to be luetic, untreated but with negative Wassermann (?) and achylia. The roentgen-ray examination showed an extremely contracted antrum. Gastroscopy in this patient showed all normal folds and markings effaced and the surface of the mucosa granular, superficially ulcerated in places and hemorrhagic in other areas. After anti-luetic treatment the roentgen-ray appearance of the stomach was restored to normal, but a second gastroscopy was not done.

A third case was of a 45-year old man, said to be luetic, in whom the gastroscopic appearance was practically the same, except that the antrum could not be visualized at all (because of contracture) and there was more atrophy of the mucosa. This case also showed improvement after anti-luetic treatment on roentgen-ray observation, but another gastroscopy was not done.

Moutier^{8,9} has more recently discussed pseudo-cancer of the stomach. He describes in detail six cases which appear to be carcinoma by roentgen examination but because of the history of the patient and the appearance gastroscopically, together with the response to antiluetic treatment, were finally diagnosed as forms of syphilis of the stomach. He divides these cases into the syndrome with tumor and no emaciation, dyspeptic syndrome with pronounced emaciation and the hemorrhagic syndrome.

In addition to the case to be reported, one of us (J. B. C.) has examined gastroscopically three other patients with known syphilis (one with cirrhosis of the liver). In two of these an atrophic mucosa was seen, indistinguishable from gastritis of other etiology. The third showed hypertrophic mucosal changes.

CASE REPORT

The patient is a white married male (J. W.), aged 64, caretaker for the barns of a creamery company. He first reported for examination at the Out-Patient Department of the University Hospital September 29, 1937.

His presenting complaints at that time were (1) burning and shooting pains in both lower extremities, (2) weight loss, and (3) insomnia. The pains in the ex-

tremities had been noticed first in the left foot about one and one-half years previously and had not extended to both legs until six weeks before examination, following a long automobile trip. He knew that he had gradually lost weight during the preceding year but did not know exactly how much. He had not been able to sleep well for three or four weeks. There had been no gastrointestinal symptoms except slight rectal bleeding on a few occasions, and more recently a transient attack of "gas pains." Slight dizziness had been present off and on throughout his present illness.

He had had scarlet fever at the age of 18, and fractured a bone in the right foot at the age of nineteen. Suppurating infections of the right hand had occurred twice. All teeth had been removed at the age of sixty-two. He denied knowledge of any venereal infection. He had never drunk alcoholic beverages and smoked and chewed tobacco moderately.

He was unable to give any account of his family history.

The patient was a well-developed tall white male in a fairly good state of nutrition. The abnormal findings were (1) Unequal, irregular pupils which failed to react to light, (2) a smooth tongue with a leukoplakial patch, (3) an accentuated second aortic sound with a systolic and diastolic murmur heard at the second left intercostal space, but no evidence of congestive failure, (4) large external and internal hemorrhoids, (5) moderate varicosities in both lower extremities. The pulse rate was 96, the blood pressure 110 systolic, 72 diastolic.

The following were the significant laboratory data. The urinalysis was normal. The blood hemoglobin was 51 per cent, red cell count 4,400,000, white cell count 6,600 with a normal differential count. The red cells show hypochromasia, anisocytosis and poikilocytosis. The blood Kolmer, Kline and Kahn reactions were strongly positive. Analysis of gastric secretions showed 14° free acid and 34° total acid after histamine. There was also acid response after an alcohol test meal, but on several occasions no free hydrochloric acid was found in the fasting contents. There was a small amount of blood in the stool by chemical test. The fasting blood sugar content was 152 mg per 100 cc. Spinal puncture brought out a clear fluid under a pressure of 8 mm mercury. The cell count was 1 mononuclear per centimeter. Nonne and Pandey tests were positive, Kolmer negative, Kline 2 plus. Sugar was present in the amount of 95 mg per 100 cc. Specific precipitation developed in colloidal gold solutions. The culture was sterile and a direct smear revealed no organisms.

Roentgen-ray examination of the gastrointestinal tract was reported as follows by the roentgenologist:

October 5, 1937 "Colon Normal except for a few diverticula of the sigmoid colon."

October 22, 1937 "Stomach The esophagus is normal. The barium fills the stomach and pours rapidly out, filling the cap, which is large and flaccid, and empties rapidly into the small bowel. The lower two-thirds of the stomach is diffusely narrowed and rather rigid, but shows minimal peristaltic waves. The mucosa of this region also appears somewhat abnormal. The fundal end of the stomach is elastic and dilates normally. The findings are strongly suggestive of lues of the stomach or possibly a diffuse infiltration of the stomach wall by scirrhus carcinoma (figure 1).

"Conclusion—*Limitis plastica*"

There was a dilatation of the ascending aorta seen by orthodiascopic examination. The heart measurements were 7.7 cm to the left and 4.0 cm to the right of the midline, with a total transverse thoracic measurement of 27.6 cm.

A left axis deviation but no other abnormality was observed in the electrocardiogram.

The first gastroscopic examination was done on October 27, 1937, the details of which are reported below. Beginning on November 20, 1937, 18 intramuscular injections of bismuth salicylate in oil were given at weekly intervals until April 6,

1938 The patient received no treatment from April 6 to April 20, but had four bismuth injections from April 20 to May 11 and none thereafter until May 25, 1938. He was also given potassium iodide in doses of 10 drops of the saturated solution three times daily for a period of one month starting November 19, 1937. In addition to his anti-luetic therapy he was given iron in the form of ferrous sulphate orally. By May 25, 1938, the hemoglobin had risen to 78 per cent and the red blood cells to 4,400,000.

On this regime his general condition improved progressively, and he continued to be free from gastrointestinal complaints. The second gastroscopic examination was carried out April 14, 1938 (noted in detail subsequently). Stool examination on April 18 showed no occult blood. It had been intended that the stomach be re-



FIG 1 Syphilis of the stomach

examined roentgenologically at that time, but through misunderstanding and later because of an accident to the patient this was not done.

Roentgen-ray examination of the stomach was, however, done on June 1, 1938. The report of that examination as given by the roentgenologist is as follows: "The same findings in the stomach now that were previously reported, although the walls appear somewhat more flexible, no real peristaltic waves could be demonstrated. There is a very small out-pouching of the anterior wall which may be a small crater or simply a peculiar mucosal arrangement. Findings at this time indicate some improvement of the process since the previous examination, which lends support to the diagnosis of *linitis plastica* on a luetic basis" (Figure 2).

The first gastroscopic examination (October 27, 1937) was easily carried out, with the 50° gastroscope. The lumen of the stomach was seen to be contracted

Very little air could be introduced and the walls of the stomach were at all times close to the objective. The normal anatomical landmarks such as the cardiac shelf, fundus pouch, *angulus* and *musculo-sphincter antri* were not present. All normal folds and rugations were effaced and instead broad, thick folds and indentations were seen. The mucosa was smooth and pale (anemic—hemoglobin at this time 51 per cent). The walls appeared as though stiff and infiltrated. No blood vessels were seen. The region of the antrum was seen as an oval tubular channel, funnelling down to the pylorus. The pyloric opening was of irregular shape, tending to be slit-like and appearing to be partly open. There were no waves going down the antrum as usual, but rather a total bellows-like closing movement of the entire antrum. The pylorus would occasionally contract, not apparently in response to the antral move-

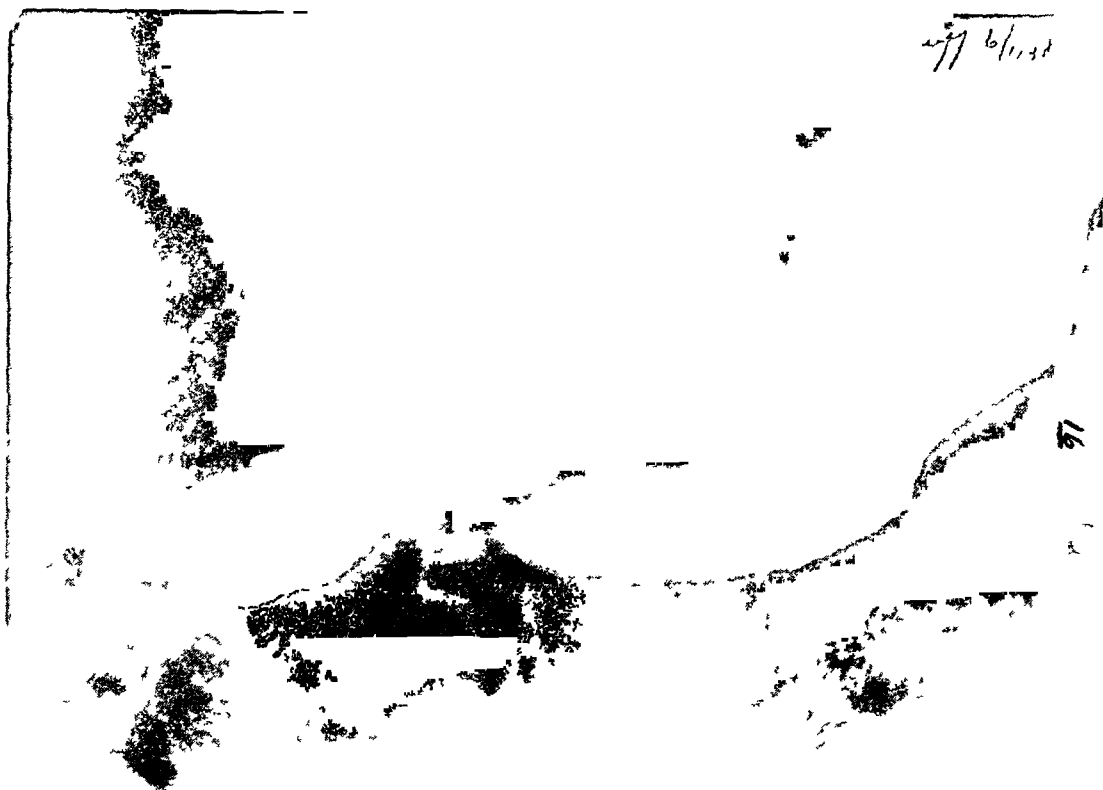


FIG 2 Syphilis of the stomach—after treatment

ments, but spasmodically, irregularly and incompletely. There were no hemorrhagic spots or ulcerations seen. The impression was that of a stiff, almost tubular structure lined with a sort of smooth pink frosting or meringue, irregularly creased and indented like an old mattress (Figure 3).

The second gastroscopic observation was made on April 13, 1938. In the interval between these two examinations the patient received iodide and bismuth therapy as noted in the case report. At this time normal anatomical features could be distinguished, that is, the *angulus*, the *musculo-sphincter antri*, the cardiac shelf and the fundus pouch. There were waves going down the antrum from the region of the *angulus* as is normally seen, and the pylorus opened and closed synchronously with these waves. There were the usual coarse folds and rugae of the greater curva-

ture and posterior wall. The mucosa was of normal color (hemoglobin was 69 per cent January 14), although it appeared somewhat thicker and smoother than usual.

A third gastroscopy was done May 25, 1938. As noted in the case report, there had been a cessation of therapy because of an accident to the patient and his consequent absence from the Dispensary. At this time the antrum was seen to be con-



FIG 3 Gastroscopic appearance of syphilis of the stomach—before treatment

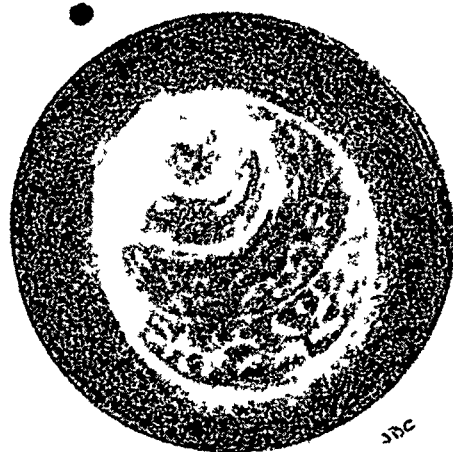


FIG 4 Gastroscopic appearance of syphilis of the stomach—after treatment

tracted, tubular and with the pylorus appearing small, far away and somewhat stiff. The *musculo-sphincter antri* could not be identified and the angulus structure was reduced to a ring-like opening with the rim stiff and thick. The color of the mucosa was normal (hemoglobin now 78 per cent). The contractions of the antrum were irregular and the pylorus never seemed to close completely. The mucosa seemed thick and, on the posterior wall and floor of the antrum, was irregularly nodular. The

body of the stomach had also a thickened mucosa, creased in some areas, and in other places of a pavement or cobbled appearance. Near the cardia the mucosa seemed atrophic, although no blood vessels were seen. There were a few hemorrhagic spots near the cardia. Our impression was that there had been a recession toward the original appearance, that is to say, the general appearance was not as nearly normal as in second examination, but not as abnormal as when first seen (Figure 4)

CONCLUSION

In conclusion, then, we have described the condition of the stomach as seen gastroscopically in a 64-year old syphilitic man without gastric symptoms, responding favorably to bismuth and iodide therapy, and tending to regress during a period when treatment was unavoidably discontinued. The roentgenological appearance of this stomach corresponded with what has been generally called the *linitis plastica* or leather bottle type of deformity. Gastroscopically the stomach was found to be contracted, with stiff walls, smooth mucosa and obliteration of anatomical landmarks. This appearance seemed to have been partially restored to that of a normal stomach under treatment.

REFERENCES

- 1 SCHINDLER, R. Gastroscopy, Chicago University Press, 1937
- 2 RENSHAW, J. F. Lymphoblastoma of the stomach, Jr Am Med Assoc, 1936, cvii, 426
- 3 KERKHOF, A. Gastroscopy, Minn Med, 1937, xix, 647
- 4 HENNING, N. Textbook of gastroscopy, Oxford University Press, 1937
- 5 SWALM, W. A., JACKSON, C. L., and MORRISON, L. Correlation of clinical and gastroscopic findings in chronic gastritis, Rev Gastroenterol, 1936, iii, 9
- 6 GUTZEIT and TEITGE. Gastroskopie, Urban and Schwarzenberg, Berlin and Wien, 1937
- 7 MOUTIER, F. Gastroscopie, Masson et Cie, Paris, 1935
- 8 MOUTIER, F., GIRAULT, A., and SEBRAY, C. Pseudo-cancers gastriques d'origine syphilitique, Arch d Mal d l'app Digest, 1937, xxvii, 637
- 9 MOUTIER, F. Pseudo-cancers gastriques peut-etre syphilitiques, Arch d Mal d l'app Digest, 1937, xxvii, 653

COARCTATION OF THE AORTA, REPORT OF A CASE WITH ASSOCIATED ANOMALIES

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COARCTATION of the aorta is a very interesting congenital anomaly in which there is a narrowing or complete obliteration of the aorta in the region of the insertion of the *ductus arteriosus*, distal to the origin of subclavian artery. Bonnet¹ has divided this anomaly into the infantile and adult types. The infantile type consists of a diffuse narrowing of the aorta between the origin of the subclavian artery and the insertion of the *ductus Botalli*. The adult type is characterized by an abrupt constriction of the aorta a little beyond the subclavian artery, as if the aorta had been narrowed by a ligature.

* Presented at the Annual Session of the American College of Physicians, Bellevue Hospital Clinic, New York City, April 8, 1938.

From the Fourth Medical Division, Bellevue Hospital, Dr. Charles H. Nammack, Director.



FIG 1 Well nourished patient, with microcephalus

In this paper no attempt will be made to review the literature, as this has been admirably done by Abbott² and by others³ Likewise, the etiology and pathogenesis of this anomaly have been adequately discussed by these authors, and will not be considered here In presenting our case of coarctation of the aorta we wish to draw attention to the importance of associated anomalies and to stress certain diagnostic features of this remarkable condition

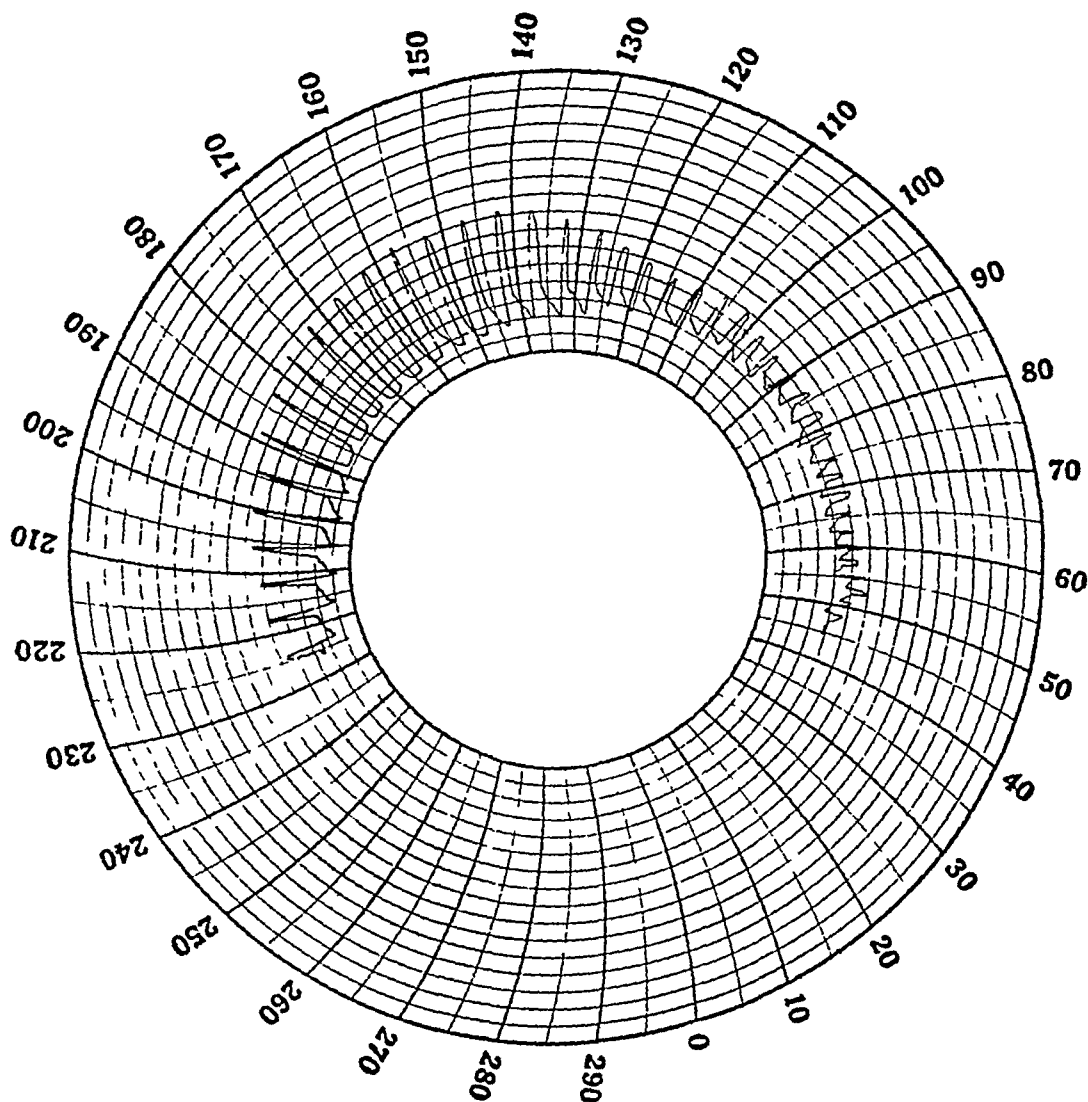


FIG 2 Oscillometric tracing of right forearm

CASE REPORT

B E, a man aged 38, entered Bellevue Hospital, March 9, 1937, complaining of pain in the left side of his chest of five hours' duration The pain did not radiate but was associated with dyspnea He had had several similar attacks during the preceding three months His past history revealed that he had been a backward child and later had been an inmate in a psychopathic institution for several years He had had some difficulty in walking as far back as he could remember

On examination the patient appeared well nourished and plethoric. His head was of the microcephalic type (figure 1). There was definite mental impairment. There was wide separation of his teeth. The lips were moderately cyanosed. The pupils reacted to light and accommodation. The chest was barrel-shaped with an increase in the antero-posterior diameter, and there was a moderate kyphosis of the dorsal spine. The lungs were clear. The heart was moderately enlarged to the left.

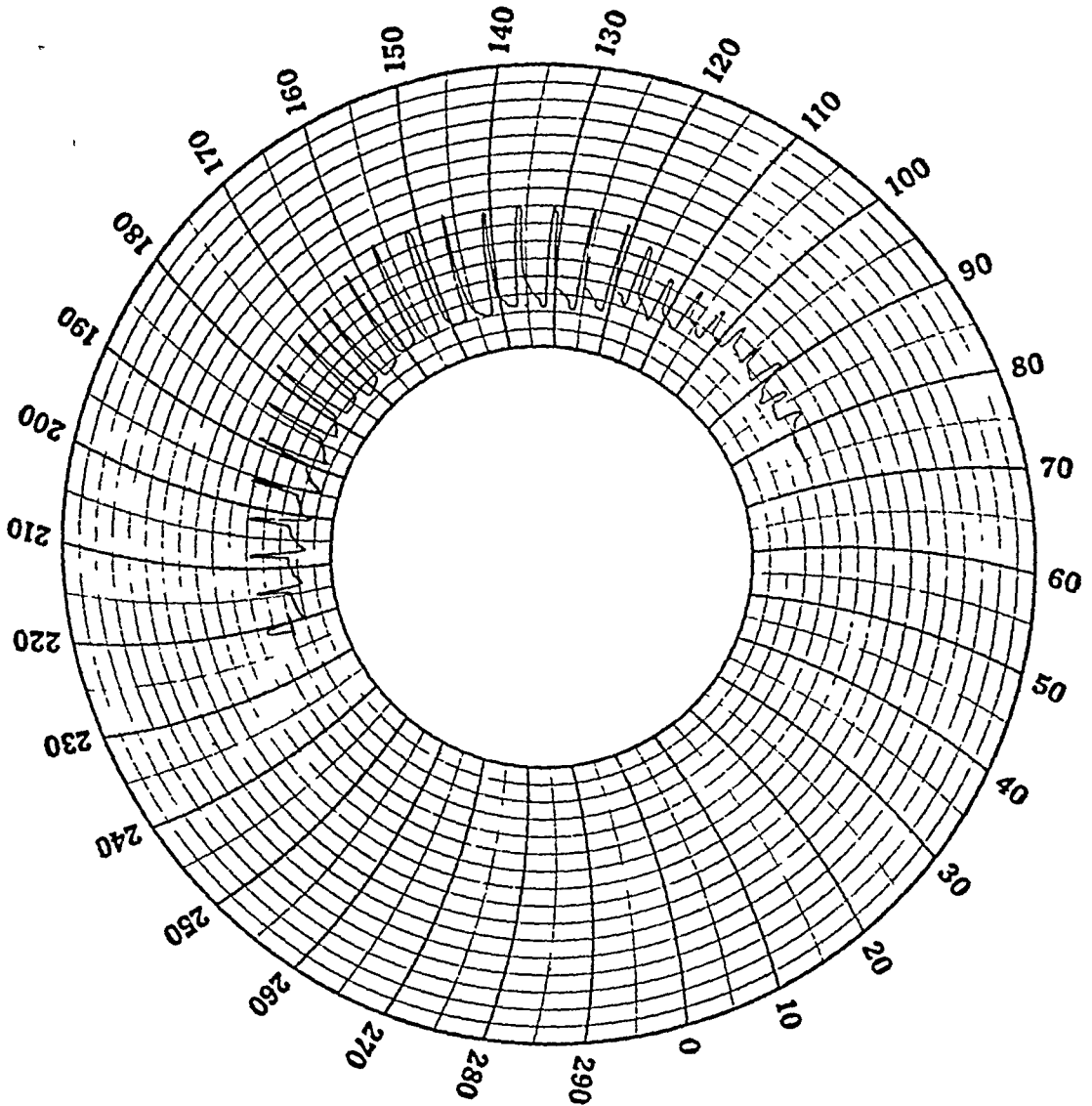


FIG 3 Oscillometric tracing of left forearm

and right. The first sound at the apex was split and followed by a harsh systolic murmur. A short systolic murmur was heard also at the base of the heart. The pulmonic second sound was greater than the aortic. The blood pressure was 180 systolic and 130 diastolic in his right arm and 204 systolic and 114 diastolic in his left arm. The abdomen was enlarged but showed no masses or fluid. The liver and spleen were not felt. The extremities appeared well proportioned in relation to his trunk. There was a small hemangioma over the outer aspect of his right heel. The femoral pulsation was feeble on both sides. There was a bilateral positive Chaddock

and a Babinski on the left side. There was no clonus. The abdominal reflexes were absent. There were no sensory disturbances. He had no ataxia, but had a waddling gait, with a tendency to drag the left foot. These neurological signs were strongly suggestive of bilateral pyramidal tract involvement, particularly on the left side. The evidence of developmental defects in a comparatively young adult with hypertension suggested to us the diagnosis of coarctation of the aorta.

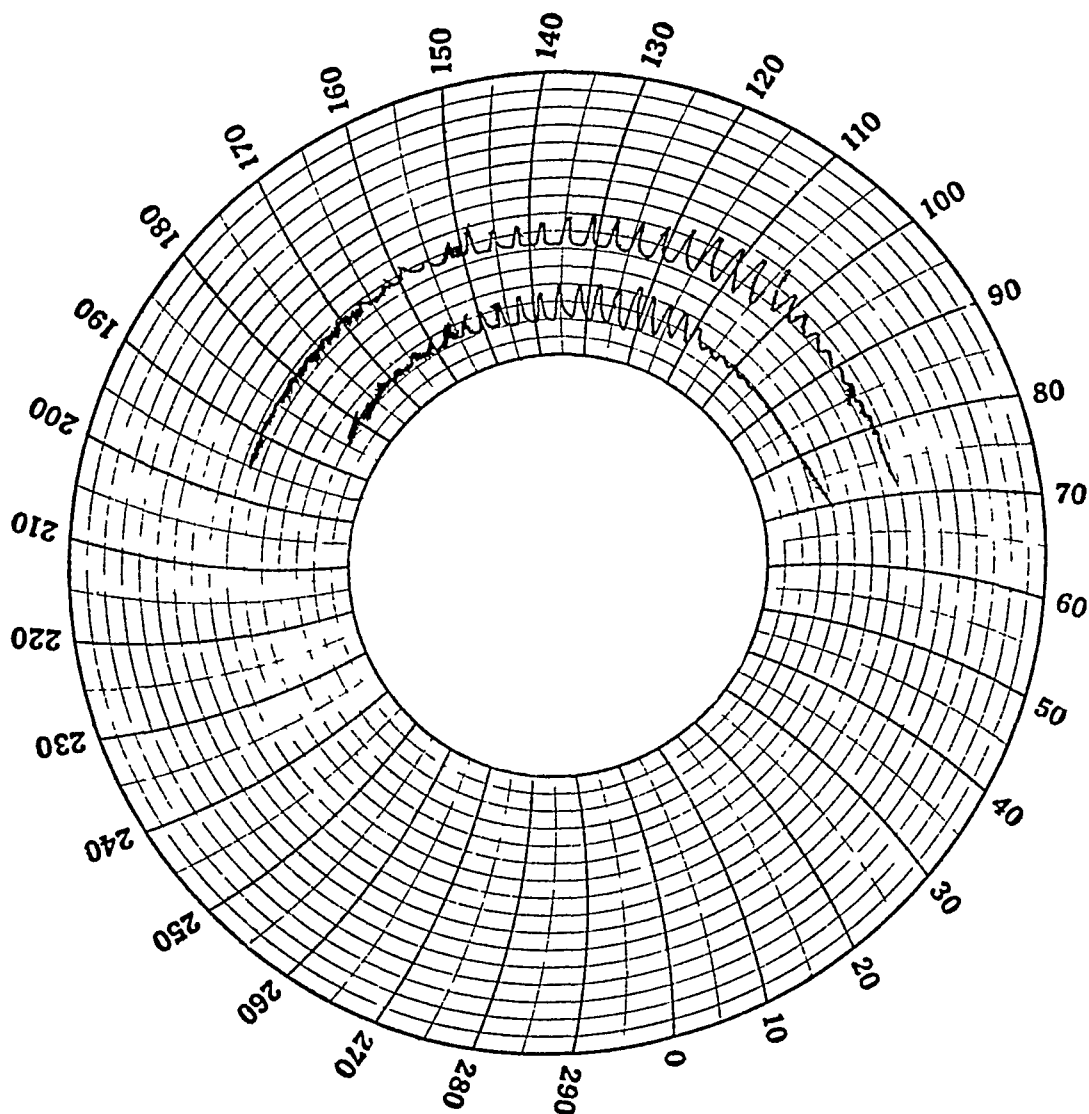


FIG 4 The upper curve is oscillographic tracing of right leg and the lower curve represents the left leg

A closer study of the patient was then made, and this revealed the presence of the characteristic physical signs of this congenital anomaly. There was marked pulsation with a harsh systolic murmur in the upper part of the interscapular region along the dorsal scapular vessels. A similar murmur was heard also over the carotid, upper intercostal, internal mammary and deep epigastric arteries. The radial pulses were full and sustained, while femoral pulsations were barely perceptible. There was marked hypertension in the upper extremities, while the blood pressure in the

lower extremities could not be elicited. The fundi showed increased tortuosity and pulsation of the retinal arteries.

Oscillometric readings revealed forceful pulsation in the arms and curves of diminished amplitude in the legs. Fluoroscopy and roentgenography showed moderate enlargement of both right and left ventricles, absent aortic knob, marked prominence of the pulmonic conus and indentation on the under surfaces of many of the ribs (figure 5). In the left oblique view the aortic arch and the descending aorta could not be visualized (figure 6). The electrocardiogram showed left axis

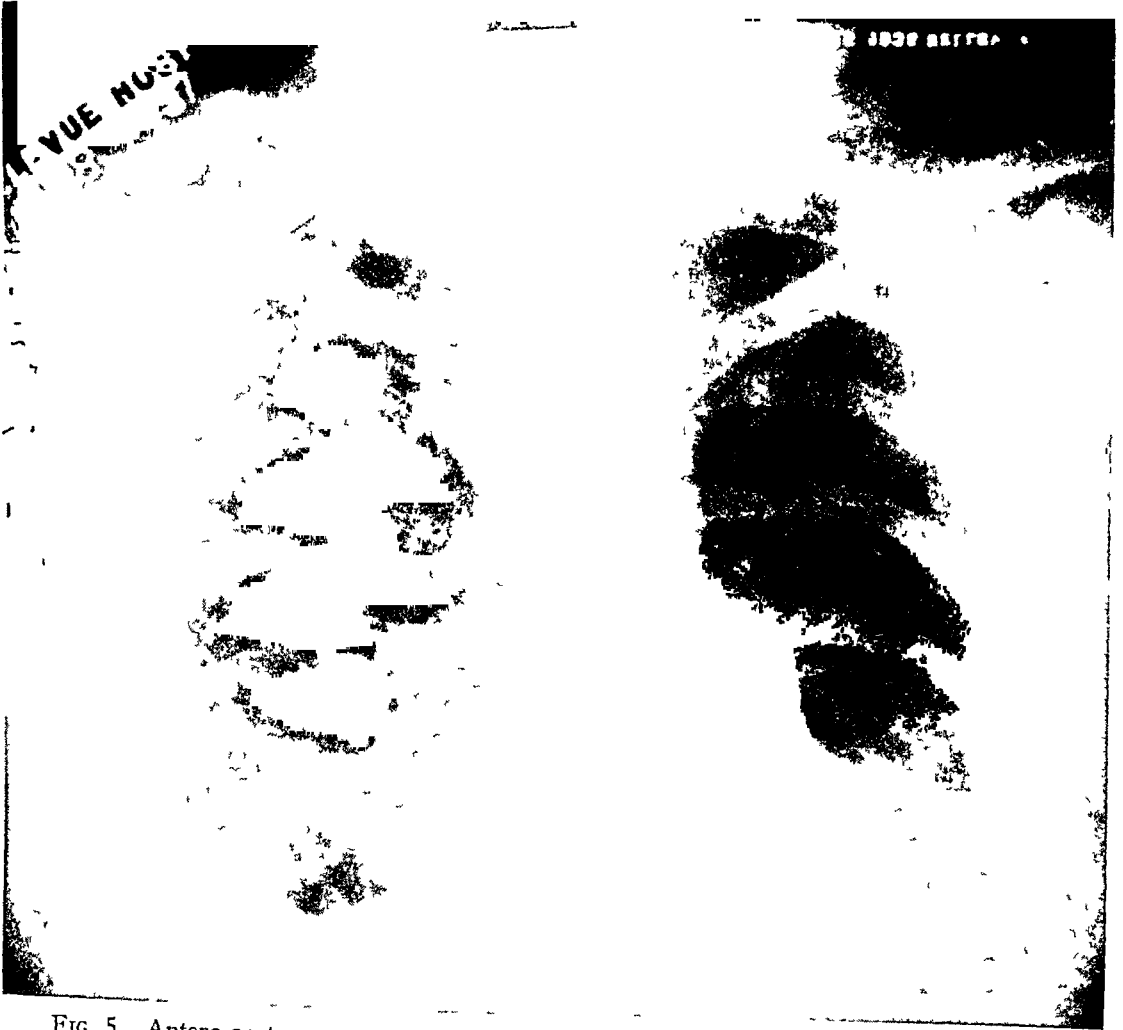


FIG 5 Antero-posterior roentgenogram of chest. Note absence of the aortic knob, prominent pulmonic conus and indentations of ribs.

deviation and deep Q-waves in Lead III. The blood count showed 4,790,000 red blood cells with 98 per cent hemoglobin and 10,200 white blood cells with 75 per cent polymorphonuclears and 25 per cent lymphocytes. The blood Wassermann was negative. The decholin circulation time was 13 seconds and ether time 6 seconds. The venous pressure was 7 cm of water. Urinalysis was negative, but a concentration test showed some impairment of function. The phenolsulphonephthalein excretion was 60 per cent in two hours. The blood chemical tests showed a non-protein nitrogen of 34 mg per cent and a sugar of 106 mg per cent. Intravenous pyelograms showed the kidneys to be of normal size and contour.

With rest in bed the patient improved and was discharged at his own request on March 19, 1937

He was re-admitted to the hospital on April 26, 1937, complaining of paroxysmal nocturnal dyspnea and of attacks of precordial pain, with radiation to the arms. The physical findings were essentially the same as those previously described. The electrocardiogram, however, showed evidence of active myocardial changes. The T-wave in Lead I was inverted and preceded by a convex shoulder. In Lead II the T-wave was diphasic and the R-T segment was convex. There were frequent premature contractions of ventricular origin. He was discharged as improved on May 6, 1937, and was subsequently observed in the Out-Patient Department.

COMMENT

This case presents a number of very interesting and important points. As previously stated, the diagnosis of coarctation of the aorta was first suspected because of the presence of external developmental defects. The presence of associated anomalies either in the heart itself or in other parts of the body has been emphasized by a number of writers on the subject. As pointed out by Abbott² the presence of such anomalies forms an interesting link in the chain of evidence pointing to developmental arrest as the chief causative factor. To the best of our knowledge, this is the first case on record in which microcephalus with impaired mentality and hemangioma of the skin were associated congenital defects. Bronson and Sutherland,⁴ however, reported a case with slight mongolianism. The presence of mental impairment is a matter of particular interest, since these subjects usually show normal, and not infrequently above average, intelligence.

The presence of associated anomalies in the cardio-vascular system has been a subject of particular interest. As pointed out first by Bonnet¹ and later by Abbott,² major or more complex anomalies are more commonly combined with the infantile type, while the minor anomalies are more frequently found in the adult form. The outstanding major anomalies are biloculate or triloculate heart, transposition of the arterial trunks and pulmonary atresia. The more important of the minor anomalies include bicuspid aortic valve, anomalous origin of the arteries from the aorta, persistent left superior vena cava, defects of the aortic septum, subaortic stenosis and cerebral aneurysms.

The enlargement of the right ventricle in our patient, and particularly the marked accentuation of the pulmonic conus suggested the presence of another cardiac anomaly. One can only speculate as to the nature of this possible additional lesion, since the patient presented no clinical signs of patent ductus, pulmonary stenosis or of other valvular or septal defects. The presence of a patent ductus arteriosus seemed to us the most likely possibility. Failure to visualize the aortic arch and descending aorta in the left oblique roentgenogram suggested also the presence of aplasia of the aorta. A similar case, with patent ductus and aortic aplasia was reported by Ulrich.⁵

Enlargement of the left ventricle is, of course, common in adult coarctation and may be due either to the hypertension or to the presence of valvular lesions produced by intercurrent infections. It is to be noted, however, that cardiac hypertrophy is not an essential feature of even the most extreme degrees of coarctation in subjects living to an advanced age.

It is difficult, if not impossible, to establish with certainty the basis of the patient's neurological signs, which were suggestive of bilateral pyramidal tract in-

volvement We have already referred to the not infrequent presence of cerebral aneurysms as an associated anomaly in cases of coarctation of the aorta These aneurysms may suddenly rupture and cause a spontaneous meningeal or cerebral

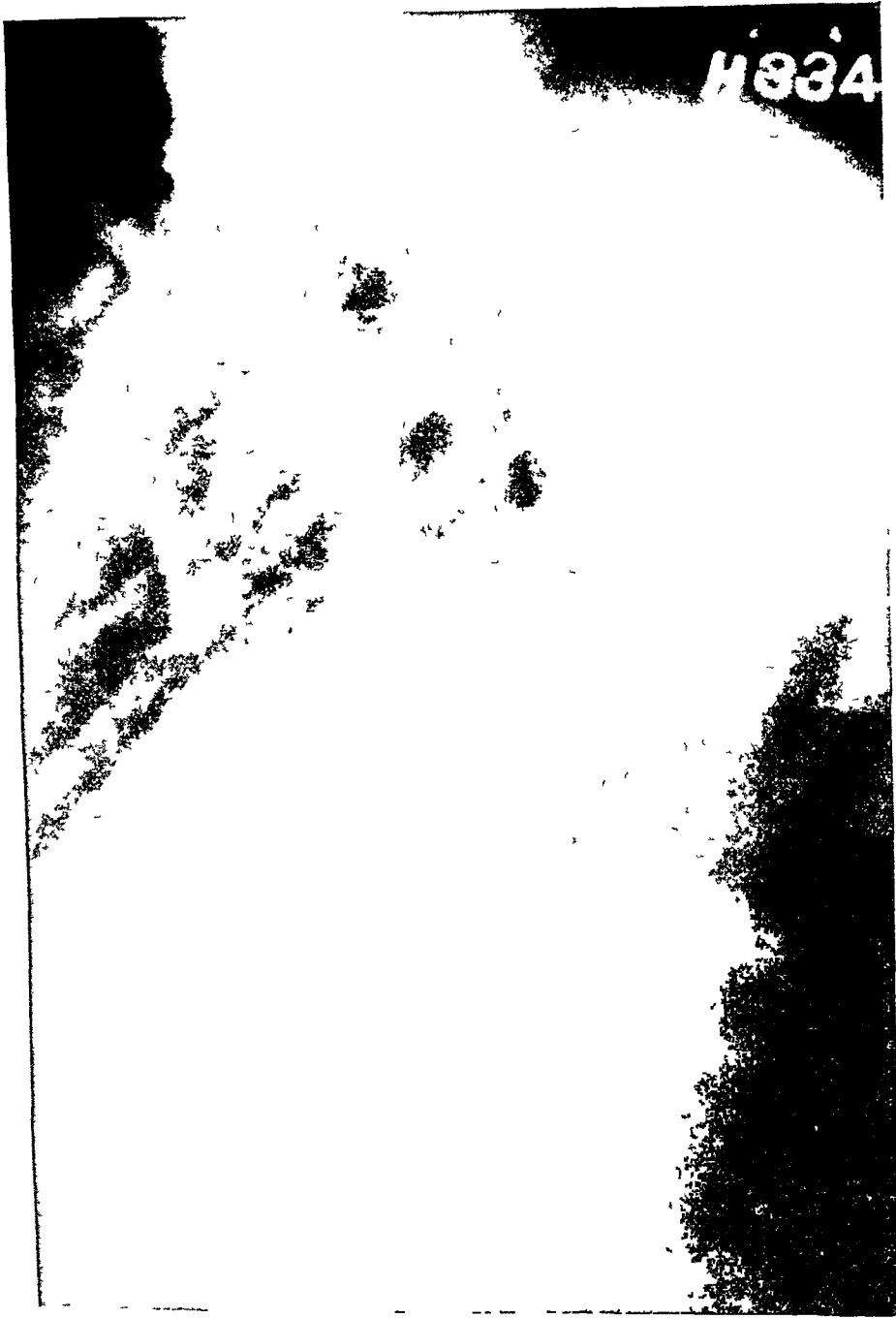


FIG 6 Roentgenogram of heart in the left oblique view The aortic arch and descending aorta cannot be visualized

hemorrhage, often leading to death In certain instances, there may be an intermittent leakage of a cerebral aneurysm, produced by the closure of a small slit-like aperture after a certain amount of bleeding has occurred, followed later

by its reopening. These patients may present alternating episodes of disturbed cerebral function and periods of relatively good health, or repeated apoplectic attacks. The phenomenon of intermittent leakage has been emphasized by several workers, notably by Parker,⁶ Lichtenberg and Gallagher⁷ and by Baker and Sheldon.⁸ It is quite possible that our patient has had episodes of intermittent leakage, although there is nothing in the history to support this assumption. One must also bear in mind the possibility that the abnormal neurological signs were due to some congenital cerebral defect associated with the microcephalus.

With regard to the history, it is to be noted that our patient's only complaints were precordial pain and dyspnea. In the great majority of cases the patients are robust young adults who have led an active life and first consult a physician when they develop symptoms of hypertensive cardiopathy. Occasionally the condition is first discovered when the patient has a cerebral hemorrhage. Rarely intermittent claudication is the presenting complaint. It is evident that coarctation of the aorta presents no distinctive symptomatology.

The physical signs of coarctation are, however, pathognomonic, and are based on the evidences of collateral circulation above the aortic constriction with diminished femoral pulsation below it. These characteristic signs may be summarized as follows:

1. A normal or bounding pulse is noted in the vessels of the neck and upper extremities, and an absence or marked diminution of pulsation, in the arteries of the lower extremities.

2. A palpable pulsation is absent in the abdominal aorta whereas a forceful systolic thrust is present in the suprasternal notch and vessels of the neck.

3. There is hypertension in the brachial arteries and a much lower or absent blood pressure in the popliteal arteries. This is a reversal of the normal state.

4. There is evidence of a well-developed collateral circulation. Large, tortuous anastomosing arteries may be seen and palpated in the interscapular, suprascapular, axillary, and precordial regions. The internal mammary and deep epigastric arteries may be dilated and palpable. A harsh blowing systolic murmur is usually heard over these collateral vessels. A thrill frequently accompanies the murmur. The features of the collateral circulation are discussed in great detail in Abbott's² comprehensive and excellent article, and need not be considered here.

5. A murmur is usually heard over the aortic area, with its maximum intensity along the left border of the sternum. This murmur is frequently modified by associated cardiac anomalies or acquired valvular lesions.

While the diagnosis of coarctation can be made on clinical grounds, the use of laboratory methods is confirmatory and frequently helpful. The difference in the oscillometric curves of the upper and lower extremities is quite striking (figures 2, 3 and 4). There are also certain characteristic roentgenologic signs (figures 5 and 6). These are as follows: (1) bilateral erosion of the inferior borders of the ribs, (2) absence of the prominent aortic knob, usually associated with hypertension, (3) narrowing of, indentation, or a gap in the descending portion of the aortic arch, which is best seen in the left anterior oblique view. Not infrequently there is also dilatation of the ascending aorta. In this con-

nection it may be noted that the electrocardiogram shows, as a rule, no striking or characteristic changes

It is evident that coarctation is not difficult to diagnose, and yet it is frequently overlooked. From Blackford's³ statistics it would seem that this condition is probably more common than is generally supposed. The possibility of coarctation should, therefore, be borne in mind when there is evidence of hypertension or hypertensive cardiopathy in a young adult without renal disease. It is important to recognize this anomaly early in order to protect these young adults from undue physical exertion.

SUMMARY

We are presenting a case of coarctation of the aorta associated with other congenital defects. Certain significant features of the associated anomalies are discussed. The cardinal physical signs of coarctation and the important laboratory findings are summarized. The importance of early diagnosis is stressed.

The authors wish to express their thanks to Dr. Gertrude H. B. Nicolson for valuable suggestions and criticisms.

BIBLIOGRAPHY

1. BONNET, L. M. Sur la lésion dite stenose congénitale de l'aorte dans la région de l'isthme, *Rev. de med.*, 1903, **LVIII**, 108, 255, 335, 418.
2. ABBOTT, M. E. Coarctation of the aorta of the adult type. II. A statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years, *Am. Heart Jr.*, 1928, **III**, 392, 574.
3. BLACKFORD, L. M. Coarctation of the aorta, *Arch. Int. Med.*, 1928, **LI**, 702.
KING, J. T. Stenosis of the isthmus (coarctation of the aorta) and its diagnosis during life, *Arch. Int. Med.*, 1926, **XXXVIII**, 69.
4. BRONSON, E., and SUTHERLAND, G. A. Ruptured aortic aneurysms in childhood with report of a case of coarctation of the adult type, *Brit. Jr. Child Dis.*, 1918, **XV**, 241.
5. ULRICH, H. L. Coarctation of the aorta (adult type). A report of three cases, *Am. Heart Jr.*, 1932, **VII**, 641.
6. PARKER, H. L. Aneurysms of cerebral vessels, clinical manifestations and pathology, *Arch. Neurol. and Psychiat.*, 1926, **XVI**, 728.
7. LICHTENBERG, H. H., and GALLAGHER, H. F. Coarctation of the aorta. anomaly of great vessels of neck and intermittent leakage of a cerebral aneurysm diagnosed during life, *Am. Jr. Dis. Child.*, 1933, **XLV**, 1253.
8. BAKER, T. W., and SHELDON, W. D. Coarctation of the aorta with intermittent leakage of a congenital cerebral aneurysm, *Am. Jr. Med. Sci.*, 1936, **CXCI**, 626.

EDITORIAL

RECENT DEVELOPMENTS IN USE AND ADMINISTRATION OF OXYGEN IN AVIATION AND THERAPEUTICS

Modern oxygen therapy can be said to have originated in the World War, through the demonstration by Haldane¹ of its great value in the treatment of soldiers who had been gassed with pulmonary irritants. His method of administration was by means of a mask but unfortunately the exigencies of war time prevented the perfection of details and the apparatus was neither comfortable nor economically efficient. Following the war, Stadie,²⁻⁴ Binger⁵ and others at the Rockefeller Institute undertook an elaborate study of oxygen therapy for those conditions in which the arterial blood was less than normally saturated as it passed through the lungs. They showed that in such conditions oxygen had great therapeutic value when administered in oxygen chambers in concentrations varying between 40 and 60 per cent. Since then the value of oxygen therapy in pneumonia, pulmonary edema and a number of other conditions has been recognized by members of the medical profession as a result of the work of many clinical investigators, especially that of Barach⁶ at the Presbyterian Hospital, New York City and that of Boothby⁷ at The Mayo Clinic.

The recent rapid development of commercial and military aviation has emphasized the dangers of the anoxemia to which pilots and passengers are exposed when flying. Barach⁸ performed a valuable public service by emphasizing the danger to the flying public of the development of even a slight degree of anoxemia in pilots. In his paper with the startling title, "Pilot error and oxygen want," he correctly emphasized the fact that a slight degree of anoxemia, even in normal healthy men, can dull the mind and judgment sufficiently to increase the chance that a pilot would make an error which would lead to a crash. When traveling at 200 miles an hour even a slowing of the mental processes, with consequent increase in the so-called "reaction

¹ HALDANE, J. S. The therapeutic administration of oxygen, *Brit Med Jr*, 1917, 1, 181-183.

² STADIE, W. C. The oxygen of the arterial and venous blood in pneumonia and its relation to cyanosis, *Jr Exper Med*, 1919, xxx, 215-240.

³ STADIE, W. C. The treatment of anoxemia in pneumonia in an oxygen chamber, *Jr Exper Med*, 1922, xxxv, 337-360.

⁴ STADIE, W. C. Construction of an oxygen chamber for the treatment of pneumonia, *Jr Exper Med*, 1922, xxxv, 323-336.

⁵ BINGER, C. A. L. The construction and management of an oxygen chamber, *Mod Hosp*, 1925, xxiv, 186-194.

⁶ BARACH, A. L. Recent advances in inhalation therapy in the treatment of cardiac and respiratory disease, *Principles and methods*, *New York State Jr Med*, 1937, xxxvii, 1095-1110.

⁷ BOOTHBY, W. M. Oxygen therapy, *Jr Am Med Assoc*, 1932, xcix, 2026-2033, 2106-2112.

⁸ BARACH, A. L. "Pilot error" and oxygen want, with a description of a new oxygen face tent, *Jr Am Med Assoc*, 1937, cviii, 1868-1872.

time," is extremely dangerous, especially if the weather is bad, visibility poor and "instrument flying" necessary. In addition, passengers who are suffering from certain cardio-respiratory difficulties, possibly without knowledge that they have such difficulties, can experience serious, sometimes even dangerous, symptoms from flying at altitudes of 5000 feet or even less, unless they are protected by efficient administration of oxygen. However, until Boothby,⁹ Lovelace¹⁰ and Bulbulian¹¹ recently reported the development by them of an oxygen inhalation apparatus of a mask type with rebreathing bag, especially designed to meet the needs of aviation, which needs include comfort, economical use of oxygen and noninterference with vision or with the use of the radio, it was practically impossible to supply oxygen routinely to both pilots and passengers. That the investigators have been successful in meeting these needs is evidenced by the satisfactory results of the severe tests to which their apparatus was subjected: first, in the laboratory, second, in the low pressure chamber at the Army Experimental Station at Wright Field, with the cooperation of Captain Armstrong and Doctor Heim, third, by actual flight tests through the cooperation of several of the commercial air-lines and noted aviators.

In addition, Boothby and Lovelace¹² have reported that the oxygen inhalation apparatus designed by them, in cooperation with Bulbulian, is applicable to the therapeutic administration of oxygen or of oxygen-helium mixtures. They pointed out that by its use not only can the ordinary inhalation of 50 to 60 per cent oxygen, such as is now generally accomplished in oxygen tents, be effected at about a fifth of the usual cost to the patient but that, in addition, higher concentrations of oxygen can be equally conveniently administered even up to the inhalation, when desired, of 100 per cent oxygen.

In a study, presented at a recent meeting of the Staff of The Mayo Clinic and Mayo Foundation, Boothby and Lovelace reported beneficial effects in the treatment of many conditions for which lower concentrations of oxygen had not proved efficient. They confirmed the report of Fine¹³ and his associates, of Boston, that inhalation of 100 per cent oxygen would, in twelve to twenty-four hours, cause decompression of an abdomen that had become distended with gas as a result of ileus or intestinal obstruction, rendering subsequent operative treatment, if the obstruction was mechanical, a much easier surgical procedure, in some instances operation was avoided.

⁹ BOOTHBY, W. M. Oxygen administration, the value of high concentrations of oxygen for therapy, Proc Staff Meet, Mayo Clin (In press)

¹⁰ LOVELACE, W. R., II. Oxygen for therapy and aviation: an apparatus for the administration of oxygen or oxygen and helium by inhalation, Proc Staff Meet, Mayo Clin (In press)

¹¹ BULBULIAN, A. H. Construction and design of the masks, Proc Staff Meet, Mayo Clin (In press)

¹² BOOTHBY, W. M., and LOVELACE, W. R., II. Oxygen in aviation: The necessity for the use of oxygen and a practical apparatus for its administration to both pilots and passengers, Jr Aviation Med (In press)

¹³ FINE, JACOB, HERMANSON, LOUIS and FREHLING, STANLEY. Further clinical experiences with ninety-five per cent oxygen for the absorption of air from the body tissues, Ann Surg, 1938, cvii, 1-13

They also confirmed the observation of Fine and his associates that in about 90 per cent of cases in which encephalography was necessary the intense headache which often follows this diagnostic procedure was either entirely avoided or the intensity of the headache was so reduced that the pain was negligible

Some of the other conditions found by Boothby and Lovelace to be benefited by the use of high concentrations of oxygen were surgical shock, gas gangrene and tetanus. They cited a case of gas gangrene in which the subcutaneous emphysema caused by the nitrogen liberated by the bacteria had extended over the trunk and up into the tissues of the neck. In this case inhalation of 100 per cent oxygen produced rapid clinical improvement, in twelve hours the emphysema was noticeably decreased, in about thirty hours the emphysema was entirely gone and the patient was progressing rapidly to recovery.

On account of the economy and simplicity of the method of administration of oxygen devised by the Rochester investigators, it will now be possible for the internist and general practitioner to use oxygen earlier than heretofore, also, it will be possible to give oxygen efficiently in the patient's home, and hospitalization, with its attendant cost, often will be unnecessary. Likewise, the use of oxygen-helium mixtures for the relief of severe asthma is rendered practicable. In view of the recent serious European complications that almost resulted in war, it will not be out of place to suggest that this method of administration of oxygen would be of great help to surgeons of the army and navy in the treatment, on a large and economical scale, of traumatic shock, of gas gangrene and tetanus resulting from infection of shrapnel wounds, of pneumonia due to epidemic influenza or to inhalation of war gases, and many other conditions.

Karsner,¹⁴ Barach¹⁵ and others demonstrated, several years ago, that concentrations of oxygen in excess of 75 to 80 per cent caused pulmonary irritation and pneumonia in small animals if administered continuously for two to three days. However, neither Fine and his associates, nor Boothby and Lovelace encountered any evidence of pulmonary irritation from inhalation of 100 per cent oxygen administered for periods varying from one to three days, followed by the use of lower concentrations in a fairly extensive series of cases. Nevertheless, patients, who receive oxygen in concentrations in excess of 80 per cent, should be carefully observed and the concentration reduced at the first sign of pulmonary irritation, for the present the continuous use of high concentrations of oxygen should not exceed 24 to 48 hours.

The advantages to be gained by the use of high concentrations of oxygen are in a new field of oxygen therapy and are due to the fact that with the inhalation of 100 per cent oxygen the amount of oxygen absorbed by the

¹⁴ KARSNER, H. T. The pathological effects of atmospheres rich in oxygen, *Jr Exper Med*, 1916, **XXIII**, 149-170.

¹⁵ BARACH, A. L. The effects of atmospheres rich in oxygen on normal rabbits and on rabbits with pulmonary tuberculosis, *Am Rev Tuberc*, 1926, **XXIII**, 293-316.

hemoglobin will be increased about 5 volumes per cent and the amount in simple solution will be increased about 7 volumes per cent, making a total increase in the amount of oxygen in the arterial blood of 10 to 15 volumes per cent. Furthermore, whenever the general or local circulation is slowed so that the percentage saturation of the venous blood falls to 20 or 30 volumes per cent the increase in the oxygen tension in the tissue spaces surrounding the cells as demonstrated by Campbell and Poulton¹⁶ may be increased by as much as 50 to 75 per cent. Such an increase in the oxygen tension in the tissues often will start an upward spiral of secondary beneficial effects which will eventuate in the patient's recovery.

¹⁶ CAMPBELL, ARGYLL and POULTON, E. P. Oxygen and carbon dioxide therapy, London, Oxford University Press, 1934, 179 pp.

REVIEWS

A Textbook of the Practice of Medicine By various authors, Edited by FREDERICK W PRICE, M D, C M, F R C P F R S (Edin) xi + 2038 pages, 14.5 × 23 cm Oxford University Press, New York, N Y Fifth Edition, 1937 Price, \$12.50

This work is a textbook of medicine, suitable for the student or physician. It follows the usual plan of most modern texts, but includes a 102-page section on diseases of the skin, a subject usually omitted from American books of this type.

The volume is almost encyclopedic in its scope, some of the sections are large enough to make up individual textbooks if published separately. Thus the division on neurology contains 390 pages, and that on the Circulation 232 pages.

The publisher has produced a remarkably compact book, as the quality of paper used compensates for the presence of almost double the usual number of pages.

There is no doubt that some chapters could be improved. Thus, hypertension, storage of lead in bones, and treatment by promoting storage, are not mentioned in the discussion of lead poisoning. Potassium restriction is not recommended in the treatment of Addison's disease, though the use of cortical adrenal extract, hypodermically or orally adsorbed in charcoal, and large doses of sodium salts, are advised. Artificial pneumothorax and phrenicectomy are recommended in the treatment of bronchiectasis. Bacteremia is not mentioned in discussing the prognosis of lobar pneumonia, nor are types IV to XXXII pneumococci separated from group IV. Serum treatment of pneumonia is said to be contraindicated in advanced age.

The English custom of recommending proprietary drugs is followed. American readers of English texts would be helped by description of such remedies according to their chemical structure, or the inclusion of U.S.P. or Council accepted equivalents. Following such a practice might increase the usefulness of English books in this country.

In spite of these objections, this work is recommended as being readable, useful, well printed, and fully indexed.

T N C

Introduction to Ophthalmology By PETER C KRONFELD, M D, Professor of Ophthalmology, The Peiping Union Medical College 331 pages, 15 × 24 cm Charles C Thomas, Springfield, Ill 1938 Price, \$3.50

This volume on "The Introduction to Ophthalmology" has the following chapter titles: "Anatomical Introduction," "The Diseases of the Anterior Adnexa of the Eyeball," "The Diseases of the Cornea," "Uveitis," "Endophthalmitis," "The Crystalline Lens," "Injuries," "The Physiology of the Retinal Circulation," "The Vascular Diseases of the Eye," "The Intraocular Pressure and its Pathological Variations," "Neoplasms," "The Optic Nerve," "The Visual Pathway," "The Pupil," "The Motor Anomalies of the Eye," and "Refraction." There is also a combined Index and Ophthalmological Dictionary.

The material in this book does not deal to any extent with details of diagnosis, methods of examination or of treatment but, as the author states in his preface, chiefly with pathogenesis of ocular disease. Points in the anatomy and embryology of the eye are reviewed where this is found necessary to a clear understanding of the facts being presented. While the author offers his book chiefly as a supplement to short practical courses in ophthalmology, it will be found valuable to all interested in diseases of the eye.

H F G

The Troubled Mind By C S BLUMH, M D 520 pages, 14 × 21.5 cm Williams and Wilkins Co, Baltimore 1938 Price, \$3.50

The book is composed largely of psychopathology from its purely descriptive point of view. The author has collected some very interesting case material which he has presented from the standpoint of objective observations. This feature is excellent, the cases are presented concisely and interestingly. The author is particularly to be commended for his remarkable facility of exposition.

Aside from the aspect of descriptive psychiatry the book remains entirely superficial. As etiological factors in the production of mental disorder the author leans extremely to the position of "stress reactions" detailing specifically such items as broken engagements, divorce, bereavement, illness, pregnancy childbirth, etc. The author shares the opinion of many institutional psychiatrists that mental breakdown occurs under the influence of added stress on some individual who is suffering from the vague malady known as "constitution." Early childhood stresses are minimized by the author. He even goes so far as to say (p. 67)

"childhood influences do not always have the significance which patients attribute to them. The facility of the procedure may permit the patient to overlook his inborn tendencies to specific types of response."

The author devotes a chapter to a discussion of infantilism and another to psychopathic or what he terms "infantoid" behavior. The terms are applied to the emotional rather than to the physical development. The only feature of unwholesome family influence that the author speaks about is that of overprotection. He refers to defective training from lack of discipline and to the inability of parents to allow children to do things for themselves. He fails to mention, however, the more vicious forms of parental attitudes embodied in neglect and rejection. No mention is made by the author of the need for emotional security and parental affection.

The author uses the trump card of "constitutional psychopathy" to explain many forms of aberrated behavior. His attitude towards these problems is that they consist of biological inadequacies in certain human beings. He believes that these are developmental defects in such individuals which are entirely unremediable. The only solution that society has to offer is to remove such persons from its midst. He goes on to quote such cases giving specific instances of behavior problems in children seven and eight years of age. It is the reviewer's impression that the author considers such cases as hopelessly "psychopathic," and beyond the realm of therapeutic assistance. That such a position is absurd goes without saying.

The book is obviously written to interest lay as well as professional readers. It appears somewhat too elementary for medical students (though perhaps not for some general practitioners), yet should prove interesting reading for them. The title may interest readers who already have some emotional conflicts. This can only lead to greater confusion because of the vivid descriptions of so many cases which might prove distinctly fear provoking. The author offers very little for the disturbed reader. Such advice as that "the patient should endeavor to tranquilize his life" seems to the reviewer to be quite futile in the face of a disturbing neurosis.

H W N

Nursing as a Profession By ESTHER LUCILE BROWN, Dept. Statistics, Russell Sage Foundation 120 pages, 13.5 × 20 cm Russell Sage Foundation, New York 1936

The Evolution of the Profession of Nursing might have been the title of *Nursing as a Profession*, one of a series of the Russell Sage Foundation monographs "dealing with the status of certain established or emerging professions in the United States."

In this monograph, Esther Lucile Brown has assembled data from various sources to show the factors responsible for the present status of nursing. The assembled facts are, on the whole, encouraging in their indication of the rise in degree of effectiveness in nursing service. Although the maximum degree of effectiveness has not been reached, the tendency is toward the rise rather than otherwise.

The interpretation given the facts presents a clear case that some branches of nursing are a profession by the six criteria set down in 1915 by Dr. Abraham Flexner who was under the impression that nursing could not meet these criteria. Approaching the answer to the question, "Is Nursing a Profession?" through evolution, the author concludes that "Nursing is moving in the same general direction as have medicine, law, dentistry, and teaching" and that "like these older professions, the personnel of each type of nursing service exhibits varying degrees of ability to accept responsibility. Such a situation, however, does not preclude recognition of professional status for the group as a whole."

One of the factors responsible for the present degree of effectiveness reached by nursing, the monograph considers "Preparation for Nursing" and the problems incident to it. The evolution of the training shows how its field of service has widened as well as its quality of service improved. From the beginning of hospital training in the nineteenth century to the twentieth century Schools of Nursing, University Schools, and Postgraduate Courses is a story of rapid evolution.

The other factor responsible for its present status of effectiveness is the four national organizations: American Nurses' Association, National League of Nursing Education, National Organization for Public Health Nursing, American Association of Collegiate Schools of Nursing.

The problems are those of supply and demand, distribution, salaries, and need for improvement in the preparation of nursing personnel for public health nursing as well as institutional nursing.

That a large part of the public fails to obtain competent nursing at the time and place necessary is because of unequal distribution in rural areas and also the infrequent "training in such specialties as psychiatry, neurology, and communicable diseases."

Besides these difficulties which nursing presents to the public, there are those to its own personnel due largely to the failures of the training "to emphasize sufficiently prevention of disease, public health nursing, or other forms of nursing given on an organized group basis to the community."

Under "Recommendation of Two Current Studies"—*Essentials of a Good School of Nursing* and *Curriculum for Schools of Nursing*—the writer presents the two studies which are based on opposite philosophies of education but reach the same conclusion or, at least, have the same tendencies in curricula for Schools of Nursing. The former centers interest on the welfare of the public—"a School of Nursing is for the patient's sake." The latter centers interest on the welfare of the nurse—"a School of Nursing is for 'aiding prospective nurses to adjust themselves to various social and professional situations.'" The difference in educational philosophy behind the two studies is more apparent than real, for both show tendencies toward the improvement of the personnel of nursing.

Under "Needed Means for controlling Standards" the monograph presents three suggested means: "A national society for accrediting schools of nursing, more adequate state legislation, a national council of state board of examiners."

Many believe that if a National Council of Nursing examiners was created, "it would lead to the evolving of more uniform requirements of nursing education, and to the harmonizing of the laws and licensure regulations of these several states."

A C

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members

Reprints

Dr Oscar W Bethea, F A C P , New Orleans, La —nine reprints
Dr Richard E Chung, F A C P , Memphis, Tenn —one reprint,
Dr Ralph M Fellows, F A C P , Osawatomie, Kan —one reprint,
Dr Hyman I Goldstein (Associate), Camden, N J —one reprint,
Dr Louie Limbaugh, F A C P , Jacksonville, Fla —one reprint,
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Dr Leo V Schneider, F A C P , Glenn Dale, Md —one reprint,
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Dr Charles W Waddell, F A C P , Fairmont, W Va —one reprint,
Dr James L Wade (Associate), Parkersburg, W Va —one reprint,
Dr Charles E Watts, F A C P , Seattle, Wash —one reprint,
Dr Edward E Woldman (Associate), Cleveland, Ohio —one reprint

Grateful acknowledgment is also made of the gift to the College Library by the Medical Protective Company of Wheaton, Ill , of a complete set of "Doctor and the Law," beginning with Volume I, No 1, and continuing through Volume V, No 2

A C P BOARD OF REGENTS TO MEET

The Board of Regents of the American College of Physicians will hold a special meeting at the College Headquarters in Philadelphia, December 18, 1938 Various committees of the College and the American Board of Internal Medicine will meet also at the College Headquarters on December 17 Important among the committee meetings will be those of the Committee on Credentials, for the examination of candidates for Associateship and Fellowship, and the meeting of the Committee on Future Policy for the Development of Internal Medicine The latter committee is responsible for the extension of old activities of the College and for all new activities

According to the By-Laws, proposals of candidates must be filed at least 30 days in advance of action Members having candidates to present for action at this meeting should have their proposals filed with the Executive Secretary of the College by November 19

Dr Carl J Wiggers, F A C P , Professor of Physiology of the Western Reserve University School of Medicine, Cleveland, sailed from New York on September 9 for Valparaiso, going thence to Argentina He was scheduled to deliver a series of lectures as follows October 17, before VI Congreso Nacional Medicina at Cordoba, October 20, Medical School, Cordoba, October 24, Medical School, Rosario, October

25, Medical School, Buenos Aires, October 26, Sociedad Argentina de Cardiologia, Buenos Aires, October 28, Academy National de Medicina, Buenos Aires

In connection with the centennial celebration of Duke University, formerly Trinity College, Durham, N C, the School of Medicine held a Symposium on Medical Problems, October 13, 14 and 15, 1938 Dr Wilburt C Davison, F A C P, Dean of the School of Medicine, presided The following Fellows contributed to the program Dr George W McCoy, New Orleans, La, "Leprosy in the United States", Dr Charles F Craig, New Orleans, La, "Amebiasis", Dr Albert Markley Snell, Rochester, Minn, "Tropical and Non-Tropical Sprue (Chronic Idiopathic Steatorrhea) Their Probable Interrelationship"

The New York Post-Graduate Medical School sponsored a Symposium on Chronic Ulcerative Colitis September 23 Dr Philip Manson-Bahr, Director of the School of Tropical Medicine and Senior Physician at the Hospital for Tropical Diseases in London, was the guest of honor and principal speaker

Dr A F R Andresen, F A C P, Brooklyn, was the leader of the discussion on "Clinical Approach to the Problem of Ulcerative Colitis", Dr Z Bercovitz, F A C P, New York, presented a paper on "Diagnostic Significance of Cellular Exudate Studies in Ulcerative Colitis," which paper was discussed by Dr Ward J MacNeal, F A C P, New York, Dr Moses Paulson, F A C P, Baltimore, gave a paper on "Diagnostic Methods in Ulcerative Colitis," and Dr J Arnold Bargen, F A C P, Rochester, Minn, gave a clinic on ulcerative colitis

Dr J C Geiger, F A C P, Director of Public Health of the City and County of San Francisco, recently received a citation "for services of distinction in the field of public health" by His Majesty, the King of Italy and Emperor of Ethiopia, who also conferred upon Dr Geiger the Cross of Cavaliere of His Order of the Crown of Italy

Dr Edward Kupka (Associate), Olive View, Calif, for the ensuing year will be a Fellow at the Forlanini Institute, Rome, Italy, studying tuberculosis He is on leave of absence from the Olive View Sanatorium

Mr Horace Trumbauer, Philadelphia architect, who designed the building now occupied as headquarters by the American College of Physicians, and many other important buildings in Philadelphia such as the Jefferson Medical College and Curtis Clinic, the Racquet Club, Philadelphia Free Library, etc, died September 18, 1938

Dr Leo V Schneider, F A C P, Glenn Dale, Md, was recently appointed Associate Clinical Professor of Medicine at Georgetown University School of Medicine, Washington, D C

Dr Reid R Heffner (Associate), formerly of the Mayo Clinic, is now located in New Rochelle, N Y, and engaged in private practice He was recently appointed Clinical Director of the Grasslands Hospital at Valhalla, N Y

The Homeopathic Medical Society of the State of Pennsylvania held its Seventy-Third Annual Session at Skytop, Pa., September 20 to 22, 1938, under the presidency of Dr. G. Harlan Wells, F. A. C. P., and the secretaryship of Dr. Donald R. Ferguson, F. A. C. P., both of Philadelphia

Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been elected corresponding member of the Royal Italian Society of Gastro-enterology, Rome, Italy

Dr. C. W. Waddell, F. A. C. P., Fairmont, W. Va., President of his State Medical Society, was recently appointed to the State Advisory Board of the West Virginia Department of Public Assistance

Dr. Hugh B. Campbell, F. A. C. P., Norwich, is President and Dr. Joseph I. Linde, F. A. C. P., New Haven, is President-Elect of the Connecticut State Medical Society

Dr. Arthur C. Christie, F. A. C. P., formerly president of the Medical Society of the District of Columbia, is the second recipient of the Frank E. Gibson Award in recognition of "meritorious contributions to medical science." The prize is presented by the Washington Medical and Surgical Society. Dr. Christie formerly was professor of operative surgery and roentgenology at the Army Medical School, professor of radiology, George Washington University Medical School and professor of clinical radiology at Georgetown University Medical School. In 1937 he was president of the fifth International Congress of Radiology, held in Chicago. He has also been president of the American Roentgen Ray Society and the American College of Radiology

Col. Charles F. Craig, F. A. C. P., Medical Corps, U. S. Army, retired, has been made professor emeritus of tropical medicine at Tulane University School of Medicine, as of September 1. He is Editor of the *American Journal of Tropical Medicine* and Associate Editor of the *American Journal of Parasitology*

Dr. Solomon Katzenelbogen, F. A. C. P., who has been associate professor of psychiatry at Johns Hopkins University School of Medicine, Baltimore, for several years, has accepted the appointment as director of laboratories and research at St. Elizabeths Hospital, Washington, D. C. Dr. Katzenelbogen graduated in medicine from the University of Geneva in 1918. He served as head of the laboratory of internal medicine, Medical Faculty, University of Geneva, and chief resident physician to the Hospital Canton, Geneva, he had been a member of the faculty of Johns Hopkins University since 1928 and has been in charge of the department of internal medicine at the Phipps Psychiatric Clinic in Baltimore

Dr. James D. Bruce, F. A. C. P., Vice President in Charge of University Relations and Director of the Department of Postgraduate Medicine, University of

Michigan, Ann Arbor, delivered the postgraduate convocational address before the seventy-third annual meeting of the Michigan State Medical Society, Detroit, September 19 to 22, on "The Challenge of Medical Service"

Dr Bruce delivered the banquet address before the Upper Peninsula Medical Society at Sault Ste Marie, held during August, his subject being, "A Doctor's Inventory"

Dr Charles A Doan, F A C P, Columbus, has been elected secretary of the Ohio Public Health Association

Dr Hans Lissner, F A C P, San Francisco, and Dr Edwin G Bannick, F A C P, Seattle, were among the guest speakers who addressed the forty-sixth annual meeting of the British Columbia Medical Association at Victoria, B C, September 15 to 17, their subjects being "Masculinizing Syndromes, Clinical Observations on the Present Status of Gonadotropic and Sex Hormone Therapy, Indications for and Proper Use of Thyroid Substance" and "Acute Pancreatitis, Medical Treatment of Severe Burns," respectively

Dr Edgar Mayer, F A C P, of Cornell University Medical College, New York, is a member of the committee appointed to supervise an intensive campaign against tuberculosis, as provided for in an appropriation of one million dollars by the Cuban government. Clinics have been established in Havana and Oriente, staffed by tuberculosis experts, and these clinics will eventually be extended through all sections of Cuba. Tuberculin tests will be given to adults as well as children, the survey being aimed especially at testing school children, tobacco workers and food handlers. Provision will be made for the hospitalization and treatment of those found to have tuberculosis

Dr Edgar V Allen, F A C P, Rochester, Minn, and Dr James G Carr, F A C P, Chicago, Ill, addressed the second annual symposium on occupational disease under the auspices of the department of industrial medicine of Northwestern University Medical School at Chicago, September 26 to 27

Dr Louis A Van Kleeck (Associate), Manhasset, N Y, is vice president of the New York State Association of School Physicians

Dr Harry A Brandes, F A C P, Bismarck, is president-elect of the North Dakota State Medical Association

Dr George R Wilkinson (Associate), Greenville, S C, has been reappointed to the State Board of Medical Examiners for four years

Capt Harry G Armstrong (Associate), Medical Corps, U S Army, addressed the tenth annual meeting of the Aero Medical Association of the United States at Dayton, Ohio, September 2 to 4, on "Effect of Acceleration on the Living Organisms"

Dr Paul J Connot F A C P Denver, has been appointed chairman of a committee to work out the details of a central service bureau to meet the demand for prepayment care, as approved by the Medical Society of the City and County of Denver This Society also approved the plans of the recently incorporated Colorado Hospital Service Association

Dr George C Stucky, F A C P formerly superintendent and medical director of the Ingham Tuberculosis Sanatorium, Lansing Mich has been appointed director of the Eaton County (Mich) Health Department

Dr George A Harrop F A C P, formerly associate professor of medicine at Johns Hopkins University School of Medicine has accepted an appointment as director of research of the Squibb Institute for Medical Research, "creating in the medical and biological fields an industry-supported research enterprise" A new laboratory building has been completed at a cost of \$750,000 Dr Harrop will be in direct charge of the Institute and in addition will head the division of experimental medicine There will be three main divisions pharmacology, bacteriology and virus diseases and organic chemistry There will also be a biochemical laboratory and a medicinal chemistry laboratory The Institute was officially opened October 11, with a special program Dr George R Minot F A C P, Boston, and Dr Russell M Wilder F A C P, Rochester, Minn, as guest speakers, spoke on "Clinical Investigation" and "Industrial Laboratories and Clinical Research," respectively

Among promotions recently announced on the Faculty of Western Reserve University School of Medicine, Cleveland, are the following

Dr Harold Feil, F A C P, Associate Clinical Professor of Medicine,
Dr Edward H Cushing, F A C P, Assistant Clinical Professor of Medicine,
Dr Harley A Williams, F A C P, Assistant Clinical Professor of Medicine

Dr John B McAlister, F A C P Harrisburg, Pa, was recently honored by a dinner by the Ex-Residents Association of the Harrisburg Hospital, celebrating the fiftieth anniversary of his internship Dr David Riesman, F A C P, Philadelphia, was one of the speakers Dr McAlister graduated from the University of Pennsylvania School of Medicine in 1887 He is an honorary life member of staff of the Harrisburg Hospital and a Trustee of Gettysburg College

Dr Bruce H Douglas (Associate), Detroit, has been in the Hawaiian Islands during the past summer, making a survey of the tuberculosis situation there

Dr Eugene R Whitmore, F A C P, Washington, D C, is secretary of the American Association for the Study of Neoplastic Diseases

Under the presidencies of Dr Paul H Ringer, F A C P, Asheville, N C and Dr Jesse D Riley, F A C P, State Sanatorium, Ark, the annual meeting of the Southern Tuberculosis Conference and the Southern Sanatorium Association was held in Louisville, Ky, September 19 to 21

Dr Henry Chesley Bush, F A C P , Livermore, Calif , is president of the National Tuberculosis Association

Dr Thomas R Brown, F A C P , associate professor of medicine at Johns Hopkins University School of Medicine, Baltimore, and Dr Beverley R Tucker, F A C P , emeritus professor of neuropsychiatry, Medical College of Virginia, Richmond, are members of a medical advisory board of a new 100 bed hospital for crippled children, started October 1, near Wilmington, under the auspices of the Nemours Foundation for Crippled Children Children up to the age of sixteen years will be admitted to the hospital, but may be kept for educational purposes beyond that age, if necessary The Foundation was provided in the will of the late Alfred I du Pont

Dr Charles A Elliott, F A C P , Chicago, addressed the eighty-ninth annual session of the Indiana State Medical Association at Indianapolis, October 4-6, on "Management of Pneumonia"

Dr Rock Sleyster, F A C P , Wauwatosa, Wis , president-elect of the American Medical Association, was a speaker at the annual banquet of the Association, presided over by Dr Herman M Baker, F A C P , Evansville

Dr Joseph McFarland, F A C P , Philadelphia, delivered the Caldwell Lecture September 20 before the thirty-ninth annual meeting of the American Roentgen-Ray Society at Atlantic City, his subject being, "Keeping in Step with Science"

Dr Clarence R Bennett, F A C P , Eufaula, Ala , is vice president of the Chattahoochee Valley Medical Association

The Joseph N McCormack Memorial Meeting of the Kentucky State Medical Association was held in Louisville October 3 to 6, Dr William E Gardner, F A C P , Louisville, presiding as president

Dr Charles E Sears, F A C P , Portland, has been elected president of the Oregon State Medical Society

The American Association for the Advancement of Science will hold a symposium on mental health in Richmond, Va , December 28 to 30, under the chairmanship of Dr Walter L Treadway, F A C P , Assistant Surgeon General of the U S Public Health Service There will be six sectional sessions and a general discussion session

Dr John H Musser, F A C P , New Orleans, and Dr Hugh Leslie Moore, F A C P , Dallas, addressed the fortieth annual convention of the American Hospital

Association at Dallas, September 26 to 30, on "Significant Nutritional Developments to be Considered in Institutional Food Service" and "Control of Infection in a Children's Hospital," respectively

Dr Theodore G Klumpp (Associate) has been appointed chief of the drug division of the Food and Drug Administration, U S Department of Agriculture

The Inter-State Postgraduate Medical Assembly will be held in Philadelphia, October 31 to November 4 Twenty-four members of the American College of Physicians appear as contributors to the program

The Medical Society of the State of Pennsylvania held its eighty-eighth annual session at Scranton, Pa, October 3 to 6, 1938 Sixty-eight assignments on the program were filled by Fellows and Associates of the American College of Physicians

Dr Alex F Robertson, Jr, F A C P, Staunton, Va, has been elected secretary of the Augusta County (Va) Medical Association

At the opening session of the Medical College of Virginia, September 19, announcement was made of the following Faculty promotions

Dr R Finley Gayle, F A C P, professor of neuropsychiatry

Dr Wyndham B Blanton, F A C P, has been made associate professor of medicine

Dr Beverley R Tucker, F A C P, was made emeritus professor of neuropsychiatry

Dr P S Smith, F A C P, Abingdon, Va, is president of the Southwestern Virginia Medical Society

Dr Rudolph H Kampmeier, F A C P, has been promoted to associate professor of medicine at Vanderbilt University School of Medicine, Nashville, Tenn

Dr O F Gober, F A C P, Temple, Texas, and Dr Edward H Schwab, F A C P, Galveston, Texas, are president and secretary-treasurer, respectively, of the University of Texas Alumni

Dr R J Condry, F A C P, Elkins, Dr L C McGee, F A C P, Elkins, and Dr P A Tuckwiller (Associate), Charleston, are president, vice president and secretary, respectively, of the West Virginia Heart Association

OBITUARIES

DR FLETCHER JOHNSTON WRIGHT

Dr Fletcher Johnston Wright was born in Fluvanna County, Virginia, in 1873, and died, after a brief illness, at his home in Petersburg, Virginia, May 8, 1938. He was graduated from the University College of Medicine, now the Medical College of Virginia, in Richmond, Virginia, in 1898, and spent the greater part of his professional life in the city of Petersburg, Virginia.

Dr Wright was a man of high character, generous impulses and attractive personality and was greatly beloved by his fellow physicians. As a practitioner of medicine he was highly regarded by his colleagues and looked upon as one of the most competent men in his section. He was always active in the medical affairs of his community and of the State and held many important offices, the duties of which he discharged with fidelity and effectiveness. At the time of his death he was a member of the State Board of Medical Examiners, of the Executive Board of the Virginia Tuberculosis Association and Chairman of the Advisory Board to the Woman's Auxiliary of the Medical Society of Virginia. Dr Wright had also served as President of the Alumni of the University College of Medicine, President of the Petersburg Medical Faculty and Vice-President of the Medical Society of Virginia. He was a member of the American Medical Association, Southern Medical Association, Tri-State Medical Association, Southside Medical Association and Fourth District Medical Society. He was a member of the staff of the Petersburg Hospital and had been an Associate of the American College of Physicians since his election in 1925.

J MORRISON HUTCHESON, M D , F A C P ,
Governor for Virginia

DR CHARLES WILLIAM STEVENSON

Dr Charles William Stevenson, age 49, of Wichita Falls, Texas, died July 31, 1938, in a Wichita Falls Hospital, of streptococcic bronchopneumonia.

Dr Stevenson was born January 8, 1889, in Sutherland Springs, Texas, the son of Orrin E. Stevenson and Isabel King Stevenson. His academic education was received in the University of Texas, Austin, from which he was graduated with a B A. degree in 1908. He then attended the Medical Department of the University of Texas for three years at Galveston, following which he taught school one year at Victoria. Resuming his medical education, he was graduated from the University of Texas School of Medicine, in 1912. After his graduation he served an internship in the Santa Rosa Infirmary, San Antonio. Following his internship, he served as assistant physician at the Terrell State Hospital, Moody's Sanitarium at San

Antonio, Dr Greenwood's Sanitarium, Houston, and the Connecticut State Hospital at Middletown, Conn. He had lived and practiced at Wichita Falls the past eighteen years.

Dr Stevenson had been a member of the State Medical Association and the American Medical Association through the county medical societies of his various places of residence, in 1915, 1917, 1920 to 1938. After his location in Wichita Falls, he founded The Medical and Surgical Clinic and was the head of the internal medicine and diagnostic department of that organization until his death. He had been a Fellow of the American College of Physicians since 1930. During the World War, he served as a lieutenant in the Medical Corps of the U. S. Army. Dr Stevenson was a member of the staffs of the Bethania and Wichita Falls General Hospitals, being a past president of the staff of the latter institution. For the past twelve years, he was medical director of Dr White's Sanitarium at Wichita Falls. Dr Stevenson was an accomplished internist and an earnest student of medicine. He had taken post-graduate work at Washington University, the University of Pennsylvania, the University of Michigan and at many other clinical centers. He was a member of the Texas Club of Internal Medicine. He served the State Association as secretary of the Section on Medicine and Diseases of Children in 1925, and as chairman of the same section in 1937. He was vice-president of the State Medical Association in the year 1930-1931, and served the Wichita County Medical Society as president in 1932. Apart from his professional life, Dr Stevenson was active in civic affairs. He served as a director of the Wichita Chamber of Commerce in 1934 and was a member of the Wichita Club. Dr Stevenson was an outstanding physician and his untimely death cut short a life of usefulness in his profession.

M. D. LEVY, M.D., F.A.C.P.,
Governor for Texas

DR. PHILIP I. MARVEL, SR.

Dr Philip I. Marvel, Sr. (Fellow), formerly one of the pioneer practitioners of Atlantic City, N. J., but living at the time of his death with his daughter at Bethlehem, Pa., died of a heart attack while hiking in the mountains near Bushkill, Pa., September 6, at the age of 81. Dr Marvel had gone out in the mountains for a walk and when he failed to return, a searching party found him with his overcoat over his left arm and his walking cane in his right hand indicating that he had died suddenly.

Dr Marvel, the son of Emery and Miranda Hubbard Marvel, was born on a farm in Kent County, Delaware, September 15, 1856. In eleven more days he would have been 82 years of age.

He attended the public schools of Delaware and the Wilmington Conference Academy at Dover, besides receiving private tutelage to fill in the weak spots of the graded schools of that time. Following his private

tutelage and much night study, he passed a state teachers examination and taught in the Wilmington Conference Academy for nearly four years. While teaching he decided to study medicine and matriculated in the medical department of the University of Pennsylvania in 1881 from which he graduated as M D in 1884. Following his graduation in medicine, he became associated with Dr William Boardman Reed, one of the medical founders of Atlantic City, where he remained for four years.

In 1888 he practiced medicine in Washington, D C, but returned to Atlantic City again in 1890, where he remained in active practice until his fiftieth year in medicine and retired in 1934.

Dr Marvel was a great believer in post-graduate education and did much to advance himself along medical lines. He took postgraduate courses in New York, Berlin, London and Vienna, and came under the direct influence of men like Pasteur, Koch, Charcot and Lister.

At the time of the Johnstown, Pa, flood, Dr Marvel was one of the first to render medical assistance and it was due partly to this terrifying experience that the Atlantic City Hospital was founded in which he served as a member of its staff for many years.

He served as President of the New Jersey Medical Society and the Atlantic County Medical Society and was a Trustee of the American Medical Association for 18 years, as well as Vice president of the A M A. Dr Marvel became a Fellow of the American College of Physicians in 1921.

Dr Marvel married Miss Rachel Irvin, daughter of Thompson and Martha Alexander Irvin of Atlantic City, November 25, 1890. Three children were born to them—Dr Philip I Marvel, Jr, Mrs Joseph Boushall and Mrs C Cooper. Dr Marvel was one of the oldest physicians of New Jersey at the time of his death.

He witnessed the great expansion of modern medicine from its inception at the hands of Pasteur, Koch and Lister to its full development as the profession knows it today.

Beginning as he did at the bottom of the profession, and ending after 50 years of practice upon a plane much to be envied by those with far greater opportunities, his example will be difficult to surpass and his niche in life hard to fill.

CLARENCE L ANDREWS, M D, F A C P,
Governor for New Jersey

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CLINICAL AND EXPERIMENTAL OBSERVATIONS ON FOCAL INFECTION, WITH AN ANALYSIS OF 200 CASES OF RHEUMATOID ARTHRITIS

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FOCAL infection is a splendid example of a plausible medical theory which is in danger of being converted by its too enthusiastic supporters into the status of an accepted fact. Certainly the theory of focal infection has travelled a long way since it was first presented to the medical profession of America by Frank Billings¹ in his classic contribution, "Chronic Focal Infections and Their Etiological Relations to Arthritis and Nephritis." This article was published in the *Archives of Internal Medicine* in 1912 and marks the first important contribution to the subject in this country. Today, 25 years after publication of Billings' article, focal infection has come to occupy a very important place in the activities of medical and surgical practice and of the various specialties.

Many of us who originally accepted the theory of focal infection with enthusiasm have watched with interest and some trepidation its rapid development in the various fields of medicine but are now wondering if the time has not arrived for a revaluation of the whole theory. Many thoughtful students today question seriously its validity, and some are quite willing to throw it completely overboard. This is particularly true in Europe where the idea of focal infection has never met with enthusiastic acceptance. But even in America, the home of focal infection, scientific men are becoming a little wearied of the universal acceptance of a theory as though it were an established fact. For example, one of our leading pathologists has satirically described a focus of infection as "anything that is readily accessible for surgery." Another colleague recently remarked that the present medi-

* Read before the American College of Physicians, New York, N. Y., April 4, 1938.
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cal epoch would probably go down in history as the "Era of Focal Infection"

Foci of infection have been assumed to play a rôle in many diseases such as arthritis, iritis, rheumatic fever, nephritis, heart disease and bronchiectasis. However, we wish to limit our discussion to the relation of focal infection to rheumatoid arthritis, the disease with which it has been so intimately associated since the birth of the theory. For example, Billings in the article above referred to, reviewed 10 cases of arthritis in each of which he defined one or more foci of infection. All were greatly benefited or absolutely cured by removal of these foci. However, after careful reading of the histories of Billings' 10 cases, it is questionable just how many of them we would classify today as typical rheumatoid arthritis.

Not only Billings but most of the earlier writers reporting studies on the relation of focal infection to arthritis have failed to differentiate clearly "infectious" or "rheumatoid" arthritis from osteo-arthritis or various other forms of joint disease. In this paper we have included under the term "rheumatoid" only those patients who presented the picture of a chronic progressive inflammatory disease of several joints characterized in the early stages by periarticular swelling and fusiform fingers, and in the later stages by ankylosis and deformity.

In 1927 Cecil and Archer² made a report on 200 cases of "Chronic Infectious Arthritis" with special reference to the incidence of focal infection. These patients had all been studied in the Cornell Clinic at some time during the preceding five or six years. Today, 10 years later, we would probably omit many of them as not fulfilling the criteria of rheumatoid arthritis, for example, only 29 per cent of the cases in this study showed fusiform fingers, a clinical manifestation which we now consider almost pathognomonic of the disease. Infected tonsils were observed in 61 per cent, while infected teeth either alone or associated with other foci were noted in 33 per cent.¹ Miscellaneous foci including infected sinuses were noted in 15 per cent of the cases. The tonsils were removed in 28 per cent of these cases as a therapeutic measure, but only one-half were cured or improved by the operation. Of the 21 cases that had teeth extracted, seven were cured and six improved. In this study on clinic patients, focal infections appear to have been very common and the removal of foci, especially when carried out early in the disease, seemed to produce beneficial results in a good proportion of cases. At that time these figures seemed striking and to have some significance, but in view of what we now know of the nature of arthritis, it is possible that a good many cases would have shown improvement even if the foci had not been removed.

Today we are faced with a different situation. Foci of infection are being rapidly disposed of by an army of energetic surgeons. Well might we exclaim, "Where are the foci of yesterday!" Comparatively rare in private practice is the sight of a tonsil either normal or diseased. How beautifully the teeth and gums are cared for!¹ How unusual is the discovery

of a neglected case of sinusitis! And yet we still have rheumatoid arthritis with us. Certainly, in spite of all we have learned about focal infection, rheumatoid arthritis is still a very prevalent disease. It is for this reason that we wish to present a study of another 200 cases of rheumatoid arthritis from the records of the private practice of Dr. Cecil with special reference to the incidence of focal infection. All of the cases in this series have been observed within the last six or seven years, and in our opinion, form an interesting contrast to the 200 cases of infectious arthritis from the Cornell Clinic reported by Cecil and Archer a decade ago.

It is axiomatic, of course, that all infections have an original focus or portal of entry through which the microorganisms gain access to the body. The site of the portal of entry may be due to a very fleeting infection such as an acute coryza or influenza or it may be a chronic focus, such as a chronic sinus or apical abscess.

A classic example of focal infection is found in gonococcal arthritis. The posterior urethra becomes infected, with a subacute or chronic infection in the prostate or seminal vesicles. From time to time a few gonococci escape from the focus in the genito-urinary tract and when conditions of susceptibility are right, the metastatic infection appears in the joints.

The problem of establishing the relation of focal infection to rheumatoid arthritis is more difficult because of the uncertainty which exists concerning the etiology. Indeed, in our opinion there is still considerable confusion in the clinical identification of this disease, and many cases of arthritis are still being classified as "rheumatoid" which do not belong in this category. Because of this confusion in classification it is difficult to compare the cases of so-called infectious arthritis noted at the Cornell Clinic with those to be discussed.

CLINICAL STUDY

The present study is based upon an analysis of 200 consecutive cases of typical rheumatoid arthritis. No case has been included that did not fulfill the classic pattern of the disease. For example, every case in the series showed, or had shown at some time previously, several characteristic fusiform fingers which, in our opinion, are a typical manifestation of this syn-

TABLE I
Cases Studied for Focal Infection

Foci	No. of Cases	Per cent
1. Definite foci		20
<i>a</i> Tonsils	27	
<i>b</i> Sinuses	11	
<i>c</i> Teeth	2	
2. Doubtful foci		10
<i>a</i> Tonsils	2	
<i>b</i> Sinuses	11	
<i>c</i> Teeth	11	
3. No demonstrable foci	140	70

drome The sedimentation rate was accelerated in 93 per cent of these patients The agglutination reaction with a strain of hemolytic streptococcus was strongly positive in 65 per cent

In analysing these carefully studied cases we found definite evidence of infection in 20 per cent and a questionable focus in 10 per cent of the cases We were surprised to find that 70 per cent of the patients revealed no demonstrable focus of infection This high figure is in part explainable by the fact that the oral hygiene of these patients had been so carefully supervised before they came under our observation Contrast this with the high incidence of focal infection found in the clinic patients 10 years ago!

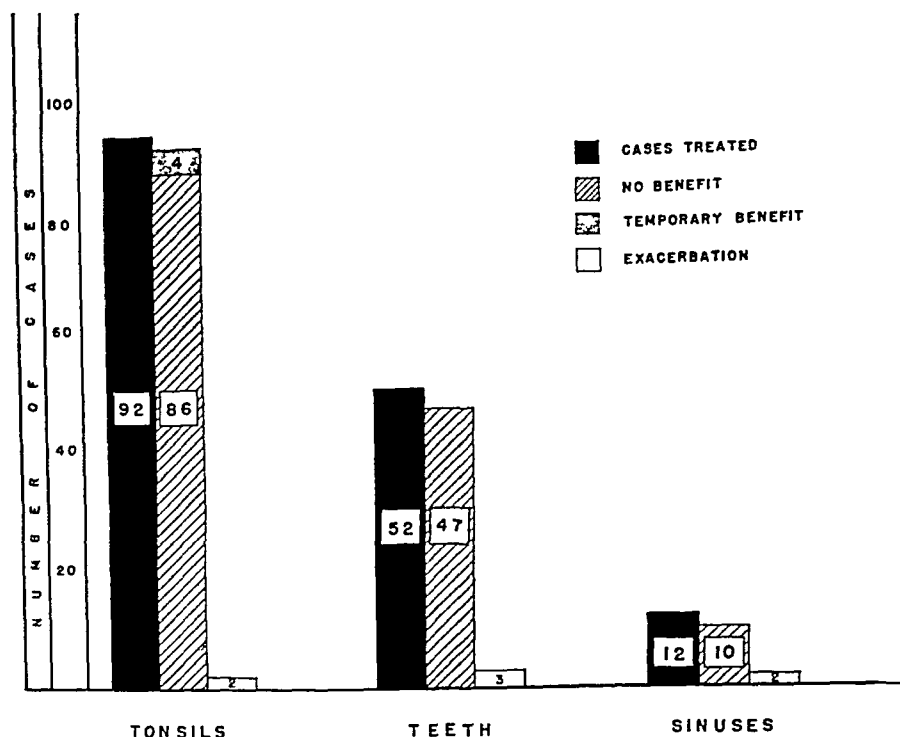


FIG 1 The results of treatment of tonsils, teeth and sinuses in a group of 200 patients with rheumatoid arthritis

Only 19 cases gave a history of an acute infection of the upper respiratory tract such as coryza, pharyngitis or influenza preceding the onset of the arthritis A smaller number of cases came on after psychic trauma, childbirth, puerperal fever, physical injury or operation

The focal infections which we have encountered in this series fall into two groups The first includes those patients that gave a history of treatment of a focus of infection before they came under our observation The second group includes the patients who, at the time when they were seen by us, had what was considered to be a focus of infection It is obvious that we cannot state with certainty how many foci in the first group were sig-

nificant However, it seemed of value to determine, if possible, the effect of removal of these foci upon the course of the disease

The organ upon which the greatest attention had been "focused" was the readily accessible tonsil The tonsils had been removed in 92, or 46 per cent, of the cases on account of arthritis although only about 15 per cent gave any history of tonsillitis or sore throat The operation had no effect upon the course of the disease in 86 cases, and caused a severe exacerbation in two instances There was temporary improvement in four cases (Figure 1) In no instance was the course of the disease arrested or the patient cured In one instance the operation upon infected tonsillar stumps appears to have been the precipitating cause of the onset of the arthritis

The problem of infection of the teeth and gums is a difficult one Fifty-two patients had had some, and in many instances all, of their teeth extracted on account of arthritis There was no benefit in 47 cases, and three patients reported a flare-up of the pain in their joints following tooth extraction

The sinuses received less attention Thirty cases gave a history of sinus disease, and 12 had been treated for sinusitis on account of arthritis before coming under our observation The treatment was of no benefit in 10 cases and in two there was an exacerbation of the disease

TABLE II
Results of Therapy

	Tonsils	Sinuses	Teeth
No of cases with infection	27	11	3
No treated for arthritis	20	5	3
No benefit	11	5	3
Benefit	7*	0	0
Exacerbation	2	0	0

* Temporary

When first seen by us 27 patients had what was considered to be an infection of the tonsils or remaining tonsillar stumps This diagnosis was confirmed in most instances by a rhinologist Twenty of these cases were treated, 13 remained unimproved or became worse, and there was temporary improvement in only 7 cases This improvement lasted from one week to several months

At the time of examination only 11 of the 200 cases gave evidence of an active sinus infection Five of these cases were treated, all without benefit

The group of patients seen by us had exceptionally fine teeth, and most of them had had periodic dental examinations so that few infected teeth were found In only three cases was additional dentistry performed There was no benefit reported in any of these cases

Other foci occurred in such small numbers that we have been unable to draw any conclusions as to their significance

EXPERIMENTAL STUDY

The experiments of Krause, Willis^{3, 4} and Freund⁵ with tubercle bacilli, and more recently those of Angevine^{6, 7} with hemolytic streptococci have shown that if bacteria are injected into a previously sensitized animal, they are fixed at the site of injection and show little tendency to disseminate from the original site. If this fact is applicable to foci of infection, one would expect little, if any, dissemination of bacteria from a well established focus.

It is apparent that no experimental work can parallel our clinical study since the etiology of rheumatoid arthritis is unknown, and the infecting agent in many of the foci is also unknown. However, since most writers believe that the tonsils, teeth and sinuses are usually infected with streptococci of various kinds, and less frequently with other organisms, the results of some experiments on rabbits to bring out the relation of focal infection to systemic disease may be of interest.

It is a well known fact that arthritis can be readily produced in rabbits by the intravenous injection of almost any strain of streptococcus. We have used a strain of hemolytic streptococcus which, when injected intravenously in small doses (2 c c) produced an arthritis in about 85 per cent of the injected animals. Arthritis appeared in one or more joints between the fourth and thirteenth day and often persisted for many months.

Using the same organism we have attempted to create foci at various selected sites. The dose of streptococcus was usually larger than that used for intravenous injection. In some animals single foci, and in others multiple foci were established. The following methods were used:

1. Suspensions of bacteria were injected into the following structures: the gum, sinus, prostate, testes, eye, pleural and peritoneal cavities, joint and skin.

2. Segments of the uterus and Fallopian tubes were isolated by ligature and injected with streptococci.

3. The renal pelvis was injected after ligation of the ureter.

4. The gall-bladder was injected after ligation of the cystic duct.

5. The animals in one group were fed large doses of streptococci over a considerable period of time.

6. Pledgets of cotton were soaked with streptococci and packed firmly into the nares where they remained for several weeks.

Blood cultures were taken in most animals at intervals of 1, 6, 24 and 48 hours after the infecting dose was given. Bacteria were usually not recovered from the blood after 48 hours. The results of these cultures gave us an indication as to how many microorganisms entered the circulation. By following the sedimentation rate and agglutination titer of the blood we were also able to obtain some evidence as to how long the focus of infection persisted. The greatest difficulty was to keep living organisms in a focus for any considerable length of time. The animals were watched

daily for the development of arthritis. They were occasionally killed when arthritis appeared but were kept in most instances for a period of two months. At the time of autopsy the focus was cultured to determine whether the injected organisms were still present, in most instances it was sterile. We were successful in establishing a focus in the eye so that we were able to recover organisms for as long as 30 days after a single intra-ocular injection. However, arthritis developed in only one instance in this group, and it appeared within six days.

Arthritis developed in only 11 of 100 rabbits. It was observed most frequently in those animals which had received injections into the gums, sinuses and male genitalia. The arthritis observed clinically was confirmed at autopsy by both gross and microscopic examination.

From these studies the following conclusions may be drawn:

- 1 Arthritis was produced in only 11 of 100 rabbits when injected by other than the intravenous route. To accomplish this it was necessary to use large doses of a suitable strain of streptococcus as well as a most susceptible animal.

- 2 Arthritis developed only in those animals from which streptococci were recovered from the blood stream shortly after injection.

- 3 In rabbits the gums were a particularly favorable site for the absorption of bacteria.

- 4 Repeated injections of bacteria caused no more arthritis than a single injection.

- 5 It was difficult to establish a chronic persistent focus of infection in rabbits.

DISCUSSION

In our introductory remarks we stressed the popularity of the focal infection theory and how this popularity had led to its very wide application in the modern practice of medicine and surgery. Indeed, focal infection has become such a fetish that the specialist feels almost duty bound to discover a focus in his chosen field when the internist, in search of a diagnosis or an explanation for certain symptoms, turns to his specialized colleague for help. This is particularly true when we attack the problem of arthritis. How often in a particular case, the internist learns from the rhinologist that the antra or ethmoid cells show a slight increase of secretion and probably are the seat of a low-grade infection. If the internist goes further in his search, the urologist may report the prostate somewhat boggy with a few leukocytes and cocci in the expressed prostatic fluid. He suggests the possibility of a low-grade infection and perhaps recommends prostatic massage. When we turn to the oral surgeon, there may be still more uncertainty. "Several of the teeth have been devitalized, the gums are retracted, and there are changes in the periodontal membrane." The dentist suggests that

such teeth are a possible source of infection and probably should be extracted

The reaction of the internist to these reports from specialists will vary according to his own platform concerning focal infection. If he is radical, he will have everything of an even suspicious nature removed. If he is conservative, he may ignore these reports completely and treat the patient instead of the focus.

The point we wish to stress, however, is that in the final analysis, these decisions should be made by the internist rather than by the specialist, and physicians should exercise a more conservative attitude regarding the treatment of tonsils, teeth and sinuses in rheumatoid arthritis than they have in the past.

The time has arrived for a complete revaluation of the focal infection theory. Undoubtedly there are cases of infectious arthritis which result from focal infection. However, as far as typical rheumatoid arthritis is concerned, it would appear from this study that chronic focal infection plays a comparatively unimportant rôle.

BIBLIOGRAPHY

- 1 BILLINGS, F. Chronic focal infections and their etiologic relations to arthritis and nephritis, *Arch Int Med*, 1912, **18**, 484.
- 2 CECIL, R. L., and ARCHER, B. H. Chronic infectious arthritis, analysis of 200 cases, *Am Jr Med Sci*, 1927, **clxxiii**, 258.
- 3 KRAUSE, A. K., and WILLIS, H. S. The rate of dissemination of virulent tubercle bacilli in normal and immune guinea pigs, *Tubercle*, 1924, **vi**, 438.
- 4 WILLIS, H. S. Studies on tuberculous infection. X. The early dissemination of tubercle bacilli after intracutaneous inoculation of guinea pigs of first infection, *Am Rev Tuberc*, 1925, **21**, 427.
- 5 FREUND, J. Retardation of tuberculous infection in guinea pigs vaccinated with killed tubercle bacilli as shown by cultural method, *Proc Soc Exper Biol and Med*, 1932, **xxix**, 1200.
- 6 ANGEVINE, D. M. The fate of avirulent hemolytic streptococci injected into the skin of normal and sensitized rabbits, *Jr Exper Med*, 1934, **lx**, 269.
- 7 ANGEVINE, D. M. The fate of a virulent hemolytic streptococcus injected into the skin of normal and immunized rabbits, *Jr Exper Med*, 1936, **lxiv**, 131.

CONCERNING THE DIFFERENTIATION BETWEEN BRONCHIAL ASTHMA VS CARDIAC DISEASE, AND POSSIBLE ILL EFFECTS FROM THE ADMINISTRATION OF EXCESSIVE AMOUNTS OF EPINEPHRINE IN THE FORMER CONDITION¹

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CASES of bronchial asthma are not infrequently encountered in which it is extremely difficult or perhaps even impossible to rule out a cardiac factor. Chronic bronchial asthma is invariably associated with varying degrees of emphysema. The latter results in permanent reduction of the vital capacity which, in some, may reach a low level. With a significant reduction of the vital capacity, shortness of breath appears on exertion, the venous pressure may be increased and occasionally dependent edema is observed. Moreover, the asthmatic attacks commonly occur more frequently and are often precipitated by exercise. Finally, it is generally agreed that the pulmonary manifestations of bronchial asthma may be indistinguishable from those of acute left ventricular failure (cardiac asthma). The following cases are illustrative of the types which present difficult problems in diagnosis.

CASE REPORTS

Case 1 A man 55 years of age complained of shortness of breath on exertion and paroxysms of intense dyspnea. This patient had his first attack of asthma when 42 years old. During the preceding two years he had experienced shortness of breath on exertion. This had gradually progressed, and on a few occasions he had noted edema of the ankles. Sleep had become more and more difficult because of the frequent occurrence of paroxysmal dyspnea. It was obvious that this patient had advanced emphysema but it was impossible to exclude a cardiac factor because of some enlargement of the heart and changes in the electrocardiogram suggestive of coronary artery disease. The vital capacity while the patient was free from dyspnea, was 2 liters (57 per cent of the estimated normal) and 23 liters after the administration of epinephrine. Death occurred 18 months later after several weeks of cardiac failure involving particularly the right side of the heart.

At necropsy there was extensive dependent edema and passive congestion of the abdominal viscera. The lungs presented an advanced stage of emphysema. The heart weighed 510 gm. There was conspicuous hypertrophy and dilatation of the right ventricle and auricle with some involvement of the left side of the heart. The coronary arteries were relatively free from arteriosclerotic changes. Histological examination of sections of the myocardium showed small areas of fibrosis but only minimal changes in the coronary vessels.

Although this patient presented cardiac failure at the time of his death, the clinical manifestations, when first seen, no doubt were due to chronic pulmonary disease.

¹ Delivered before the American College of Physicians, New York, April 5, 1938.
From the Department of Internal Medicine, State University of Iowa, Iowa City, Iowa

Case 2 A man 58 years of age was admitted to the hospital because of cough and attacks of dyspnea. He had been subject to bronchitis for years and occasionally observed wheezing in the chest. There had been shortness of breath on exertion for several months. He had recently contracted an upper respiratory infection, and on two or three occasions had been awakened from sleep by intense dyspnea. Sibilant râles were heard throughout the chest. The vital capacity was 24 liters (60 per cent of the estimated normal). There was no demonstrable increase in the size of the heart. The cardiac tones were of good quality and the blood pressure was 120 mm Hg systolic and 85 diastolic. The cardiac enlargement was verified by a teleoroentgenogram. The electrocardiogram did not reveal any significant alterations. The diagnosis was asthmatic bronchitis and emphysema.

Shortly following discharge from the hospital this patient began to notice more shortness of breath with routine physical activities and occasionally was conscious of heaviness or a squeezing sensation in the precordial region. A few weeks later he had a very severe attack of pain in the chest extending to the arms, accompanied by dyspnea so intense that morphine was required. He stated that the difficult breathing was quite similar to that experienced in the past. This patient has since had numerous attacks of paroxysmal dyspnea with wheezing in the chest, and now has advanced cardiac failure.

The age of this individual and the history naturally directed attention to the heart but the examination failed to reveal evidence of cardiac damage. In the light of the subsequent developments, however, one is inclined to question the correctness of the original diagnosis.

Case 3 A woman 61 years of age gave a history of having had hay fever occasionally accompanied by asthma, for a period of years. She contracted a cold in November which persisted for about one month. Following this she was easily fatigued. The fatigability later became more pronounced. The day after Christmas she felt unusually tired and had pain in the right hemithorax. Herpetic lesions subsequently developed. After recovering from the herpes zoster she developed another upper respiratory infection. Within a few days she began to notice shortness of breath, and later had an asthmatic-like attack. She remarked that she had never had asthma before except during hay fever season. This was fairly well controlled by the administration of ephedrine but continued to recur. Examination disclosed cyanosis, moderate enlargement of the heart, moist râles in the bases of the lungs, tenderness of the liver and edema of the ankles. Blood pressure was 190 mm Hg systolic and 110 diastolic.

It is apparent that this patient presented both cardiac failure and asthma. The occurrence of the asthmatic attacks at this time is of particular interest and will be discussed later.

In 1929 Kountz, Alexander and Dowell¹ reported a series of 66 cases of pulmonary emphysema which simulated cardiac failure. Fifty-eight of these patients presented cyanosis and complained of shortness of breath on exertion. In 18 edema was present during the period of study whereas 21 gave only a history of this finding. In all, there was 39 (59 per cent) who either showed dependent edema or gave a history of it. The vital capacity was considerably reduced in all, and in some to less than 50 per cent of the estimated normal. Nine of these patients came to necropsy. In one there was hypertrophy and dilatation of both the right and left ventricle, whereas hearts of the remaining eight patients did not present significant pathological changes. Since, in eight there was no evidence of cardiac disease, it was necessary to explain the dyspnea, cyanosis and edema on another basis. It

was pointed out that the dyspnea and cyanosis might result from the reduced vital capacity. The edema was attributed to two possible factors, increased venous pressure and anoxemia. The problem was further studied by observing the effects of experimentally induced emphysema in dogs. Extensive emphysema was produced within a period of a few weeks by means of a ball-valve in the trachea. This procedure was carried out in a series of 16 dogs. Simultaneous determinations of the intrapleural and peripheral venous pressures were made at intervals for several weeks. It was observed that as the emphysema developed, intrapleural pressure rose and that this was followed by a rise of the venous pressure. These experiments seemed to provide a plausible explanation for the increase in the venous pressure but did not reproduce the dependent edema.

The experience of Alexander and his co-workers^{1,2} would seem to indicate that the incidence of cardiac damage in long standing bronchial asthma or in cases in which pulmonary emphysema is the dominant feature is relatively low. They concluded that the heart remains singularly free from injury after continuous bronchial asthma, despite the attendant emphysema.

In most cases of chronic bronchial asthma the heart is normal in size and the electrocardiogram does not reveal any important abnormalities. Under these circumstances one is ordinarily justified in concluding that the heart is not contributing to the pulmonary manifestations despite the presence of cyanosis and increased venous pressure. When, however, there is demonstrable cardiac damage, the evaluation of this is often extremely difficult. The response to digitalis and theophylline ethylenediamine may help solve the problem. Moreover, the results obtained by circulatory measurements such as carried out by Hitzig, King and Fishberg³ and Oppenheimer and Hitzig⁴ may provide important information. In the studies by Oppenheimer and Hitzig, dealing particularly with cases presenting advanced pulmonary disease, the circulation time from the arm to the lung was determined by the ether method, and that from the arm to the tongue by the use of saccharin or decholin. The circulation time from the lung to the tongue was obtained indirectly by subtracting the circulation time from the arm to the lung from that of the arm to the tongue. These tests were devised as means of determining the efficiency of the right and left ventricles. They are simple procedures and thus may be employed in routine practice. The normal circulation time from the arm to the lung ranges from 4 to 8 seconds. With frank right ventricular failure it may be extended to 12 seconds. The normal circulation time from the lung to the tongue is said to range from 4½ to 10 seconds. In cases of left ventricular failure, however, studied by Hitzig, King and Fishberg,³ this time varied from 12 to 22 seconds.

One gets the impression from the literature that bronchial asthma and left ventricular failure rarely co-exist. Swineford and Magruder,⁵ however, have recently reported 21 instances. All of their patients gave a

history of having had asthma in a mild form for several years and presented unmistakable evidence of cardiac disease. This study is of particular interest. It was undertaken primarily to determine the significance of wheezing in patients with paroxysmal dyspnea and evident cardiac disease. They pointed out that wheezing may or may not be present in acute left ventricular failure. This manifestation was regarded as a fundamental sign of bronchial asthma and therefore allergic in nature. With this in mind, the patients with cardiac disease and wheezing were carefully studied for allergic manifestations, and a high incidence was found. On the basis of these observations the theory was advanced that the addition of wheezing to paroxysmal dyspnea is, in the large majority of cases, an indication that the patient previously had had asthma of some degree, or that he was an allergic individual in whom the onset of the asthma is provoked by the pulmonary congestion incident to the failure of the left ventricle. This conception seems to provide a plausible explanation for the asthmatic aspect of acute left ventricular failure. Case 3 is illustrative of the type studied by Swineford and Magruder. It is to be recalled that until the onset of the cardiac failure, this patient never had asthma except during the hay fever season.

The types of cases under consideration bring up the question of the use of epinephrine. There seems to be a general feeling among the allergists that this drug may be given at frequent intervals and in large doses, if necessary, and over a long period of time without any apparent ill effects. Rackemann⁶ states that he has had a number of patients who required 12 to 15 injections every 24 hours, for months at a stretch, and so far he had not observed any organic changes in these subjects. Coca⁷ reports that the prolonged and excessive use of epinephrine has no lasting influence on blood pressure and produces no demonstrable organic changes. He also points out that even though large quantities may have been required to control the asthma, after several months of freedom from asthma, prompt relief may again be obtained from a small dose.

In many of the cases in which we have had difficulty in excluding a cardiac factor, the patients have received large quantities of epinephrine and yet their condition had gradually progressed, as indicated by the following patient.

This 68 year old man had asthma during early childhood until eight years of age. He then had no further trouble of this nature until the age of 65 when, following an upper respiratory infection, he was awakened from sleep by dyspnea. For several months thereafter the paroxysms of dyspnea occurred only at night. Later, however, they appeared during the day following exertion. The attacks gradually increased in frequency until they were coming every two or three hours. During the three months previous to admission to the hospital he had received six to eight injections of epinephrine during the 24 hours. This patient was having an asthmatic attack when admitted to the hospital and was promptly given an injection of epinephrine, but did not obtain any relief. He was quite cyanotic. The skin was moist and cold and the pulse was 130 per minute and of poor quality. There was moderate emphysema. The size of the heart was difficult to determine, but a

roentgenogram taken later showed it to be slightly increased. There was a gallop rhythm. The blood pressure was 180 mm Hg systolic and 110 diastolic. An electrocardiogram showed a negative T deflection in Leads II and III. Morphine was then prescribed and the patient had a fairly good night. Thereafter the attacks were controlled by the administration of a solution of 50 per cent glucose with 0.48 gm of theophylline ethylenediamine. The effects of the medication were noticed by the patient soon after the solution was introduced into the vein and complete relief was obtained ordinarily within five minutes. After two weeks, the vital capacity had increased from 1 to 3.2 liters and the patient stated that he could breathe more easily than at any time in three years. Similar results from the use of glucose solution with theophylline ethylenediamine have been observed repeatedly in patients who have been receiving large quantities of epinephrine.

There are reasons for believing that the function of the heart may be impaired by the therapeutic use of excessive amounts of epinephrine, as suggested by the above case. Myocardial lesions have been produced repeatedly in rabbits by the intravenous injection of epinephrine^{8,9}. In the earlier experiments, a series of injections was employed. In certain instances, as pointed out by Pearce,⁸ death occurred from acute dilatation of the heart and pulmonary edema within a few minutes following the initial injection of 0.2 c.c. of 1 to 1000 solution of epinephrine. Fleisher and Loeb,¹⁰ and others,¹¹ have since shown that changes in the myocardium occur very frequently in animals following a single injection of the above amounts of epinephrine.

The action of epinephrine on the coronary vessels has been extensively studied. On the whole, the results have been very conflicting, but certain experiments seem to produce convincing evidence that there is a constricting effect.¹² This is further supported by the electrocardiographic changes induced in animals by the injection of epinephrine. In experiments recently reported by Milles and Smith¹³ and by Douglas, Giffand and Shookhoff,¹⁴ pronounced alterations were observed in the T deflection and the S-T segments. Furthermore, Douglas and his co-workers were able to abolish this effect by the administration of nitroglycerine.

Levine, Ernstene and Jacobson¹⁵ have shown that the subcutaneous administration of epinephrine in doses of 1 c.c. frequently precipitates attacks in patients with angina pectoris. While it was suggested that this drug might be employed as a diagnostic test in questionable cases, it was pointed out that it should be used very cautiously. Other observers have since called attention to the possible ill effects from the administration of epinephrine in cases of coronary artery disease. Katz, Hamburger, and Lev¹⁶ have studied the effects of an injection of 1 c.c. of a 1 to 1000 solution of epinephrine on the electrocardiogram of normal persons and patients with angina pectoris. They reported a downward deviation of the S-T segment and a reduction in the amplitude of the T-wave.

Finally, the action of theophylline ethylenediamine is of interest in this connection. This drug is commonly prescribed because of its action on the coronary vessels and is one of the most effective remedies in the treatment

of acute left ventricular failure¹⁷ It also has a favorable effect on the bronchial obstruction in asthma¹⁸ Moreover, it has been employed with success in patients who fail to respond to epinephrine,^{19, 20} as illustrated by the case previously cited Herrmann and Aynesworth²¹ have recently reported 16 cases in which theophylline ethylenediamine had been administered as an emergency measure after epinephrine had failed to give relief They state that prompt, complete and persistent relief was obtained from 31 of the 41 injections given under these circumstances It was furthermore pointed out that after treatment with theophylline ethylenediamine, the usual response to epinephrine was restored

SUMMARY

The differentiation between bronchial asthma and cardiac disease not infrequently presents a difficult problem This pertains particularly to certain of the cases with a long history of asthma and significant emphysema who have reached the age in which degenerative disease of the heart is prevalent, to those in whom the onset of the asthma occurs late in life, and to those with both chronic pulmonary disease and cardiac disease Cases illustrating each of these groups are cited Finally, it is suggested that the excessive use of epinephrine may impair the function of the heart

BIBLIOGRAPHY

- 1 KOUNTZ, W B ALEXANDER, H L, and DOWELL, D Emphysema simulating cardiac decompensation, *Jr Am Med Assoc*, 1929, *xiii*, 369
- 2 ALEXANDER, H L, LUTEN, D, and KOUNTZ, W B The effects on the heart of long standing bronchial asthma, *Jr Am Med Assoc*, 1927, *lxviii*, 882
- 3 HITZIG, W M, KING, F H, and FISHBERG, A M Circulation time in failure of the left side of the heart, *Arch Int Med*, 1935, *lv*, 112
- 4 OPPENHEIMER, B S, and HITZIG, W M The use of circulatory measurements in evaluating pulmonary and cardiac factors in chronic lung disorders, *Am Heart Jr*, 1936, *xii*, 257
- 5 SWINEFORD, O JR, and MAGRUDER, R G Asthma in heart disease, a clinical study with especial reference to cardiac asthma, *South Med Jr*, 1937, *xxv*, 829
- 6 RACKEMANN, F M Clinical allergy, particularly asthma and hay fever, 1931, MacMillan Co, New York, page 465
- 7 COCA, A F, WALZER, M, and THOMMEN, A A Asthma and hay fever in theory and practice, Part 2, 1931, Charles C Thomas, Baltimore, page 276
- 8 PEARCE, R M Experimental myocarditis A study of the histological changes following intravenous injections of adrenalin, *Jr Exper Med*, 1906, *viii*, 400
- 9 CHRISTIAN, H A, and WALKER, C Experimental myocarditis produced by spartein sulphate and adrenalin chloride, *Arch Int Med*, 1911, *viii*, 515
- 10 FLEISHER, M S, and LOEB, L Experimental myocarditis, *Arch Int Med*, 1909, *iii*, 78
- 11 GRUBER, C M, OLCH, I Y, and BLADES, B Myocarditis produced experimentally in rabbits by drugs, *Jr Pharm and Exper Therap*, 1933, *xliv*, 306
- 12 SMITH, F M Diseases of coronary arteries and cardiac pain, 1936, MacMillan Co, New York, page 119
- 13 MILLES, G, and SMITH, P W Effects of epinephrine on the heart, *Am Heart Jr*, 1937, *xiv*, 198

- 14 DOUGLAS, A H, GILFAND, B, and SHOOKHOFF, C Production by epinephrine of S-T changes in the electrocardiogram of the cat, similar to those of coronary occlusion, *Am Heart Jr*, 1937, xiv, 211
- 15 LEVINE, S A, ERNSTENE, C A, and JACOBSON, B M The use of epinephrine as a diagnostic test for angina pectoris, with observations on the electrocardiographic changes following injections of epinephrine into normal subjects and into patients with angina pectoris, *Arch Int Med*, 1930, xlv, 191
- 16 KATZ, L W, HAMBURGER, W W, and LEV, M Diagnostic values of epinephrine in angina pectoris, *Am Heart Jr*, 1932, vii, 371
- 17 SMITH, F M Treatment of left ventricular failure, *Jr Am Med Assoc*, 1937, cix, 646
- 18 GREENE, J A, PAUL, W D and FELLER, A E The action of theophylline with ethylene diamine on intrathecal and venous pressures in cardiac failure and on bronchial obstruction in cardiac failure and in bronchial asthma, *Jr Am Med Assoc*, 1937, cix, 1712
- 19 HAJOS, K Einführungen ueber Asthmatherapie, *Wien klin Wchnschr*, 1936, xlv, 737
- 20 TUFT, L Clinical allergy, 1937, W B Saunders Co, Philadelphia, page 330
- 21 HERRMANN, G, and AYNESWORTH, M B Successful treatment of persistent extreme dyspnea, "Status Asthmaticus," use of theophylline ethylene diamine (Aminophylline U S P), *Jr Lab and Clin Med*, 1937, xxi, 135

THE TREATMENT OF LIVER DISEASE^{*}

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INTRODUCTION

ATTEMPTS at treatment of parenchymatous disease of the liver other than those types which are entirely self-limited constitute a somewhat discouraging chapter in medical history. Most therapeutic procedures have been used, discarded, and readopted at intervals over a period of many years and all have failed so signally to cure or control such diseases that the present generally pessimistic attitude in regard to therapeutics is well justified. However, within recent years a great deal of valuable experimental work has been done on the pathologic physiology of the liver, indicating the tremendous reserve function of the organ and its capacity for regeneration and repair. On the basis of such observations it would seem at least theoretically possible to make a better record in treatment. The material to be presented here is not so much a record of therapeutic triumphs as it is an attempt to review recent work which holds promise of therapeutic helpfulness in cases of disease of the liver and to cite its possible clinical application.

For purposes of the discussion to follow, a definition of the conditions to be discussed seems desirable. The term "hepatic disease" as it is used hereinafter refers to chronic destructive and degenerative processes involving the parenchyma of the liver. Simple atrophy, fatty metamorphosis, and focal necrosis, either confined to the region of the central vein of the lobule or affecting the entire structure, apparently represent the fundamental lesions associated with all types of hepatic injury, whether this may be caused by biliary obstruction, infectious diseases or specific hepatotoxic agents, in that the destruction, subsequent repair, and regeneration of the liver proceed in about the same manner although not necessarily at the same rate. For instance, one may see pathologic evidence of acute atrophy of the parenchyma of the liver following calculous obstruction or stricture of the common bile duct, it may occur postoperatively after removal of the gall-bladder¹, it may be a feature of thyrotoxic crises or it may follow the use of certain hepatotoxic drugs. Finally, chronic atrophy (cirrhosis) may develop on the basis of repeated episodes of acute injury of the liver. There is, then, good pathologic evidence for the unity of most primary injuries of the liver, a point of view first held by Legg². On both clinical and experimental ground it may be said also that the general problem of protecting the parenchyma of the liver is somewhat the same in treatment of all types of hepatic injury.

There may be mentioned here some general factors which influence the

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course of hepatic injury It has been shown that the liver neither regenerates nor repairs itself in the presence of complete obstruction of the bile ducts³, similarly, regeneration does not occur if a hepatotoxic agent is still operative or if there is a marked reduction of flow of portal blood The first and second factors, of course, can be corrected in some instances although the third remains beyond present methods of control However, it is believed that compensatory changes in the circulation occur in the course of time which minimize this difficulty to some extent

DIETARY FACTORS

Since the early experience of Opie and Alford⁴ on the effects of diet on the course of hepatic injury following experimental poisoning by chloroform and phosphorus it has been known that a high intake of carbohydrate has a definite specific protective effect against hepatic necrosis This observation has been substantiated many times in a variety of experimental hepatic lesions and, on the basis of such observations, a dietary regimen for all types of hepatic disease has been agreed on generally The usual practice is to give a diet containing 350 gm or more of carbohydrate, 1 to 1.5 gm of protein for each kilogram of body weight, and an amount of fat compatible with the patient's tolerance and caloric requirements Administration of additional carbohydrate in the form of syrups, jellies, jams, candy, and sweetened fruit juice also is encouraged The difficulties in the administration of such a diet to seriously ill patients is obvious and, for this reason, additional amounts of carbohydrate in the form of glucose must be administered intravenously The use of glucose will be discussed in a subsequent section of the paper, at this time it suffices to say that there is no apparent great advantage in giving glucose by vein if the patient can take adequate amounts of carbohydrate by mouth

It has been demonstrated experimentally that the liver maintains a reasonably adequate function even on diets of widely varying composition, even under circumstances when the content of glycogen is low and fatty change is microscopically evident In other words, the diet, at least so far as the chemical composition of the liver is concerned, may be varied somewhat without loss of therapeutic effect It is apparent, however, from studies on animals and patients that the success or failure of treatment of a patient who has a severely damaged liver depends to a large extent on the patient's ability to continue to take a well balanced and ample diet over a long period

The use of concentrates of vitamins in connection with dietary treatment is discussed in a later paragraph but some reference to the subject is essential at this point The liver is known to be instrumental in the formation or storage of vitamins A, B₁, the B₂ complex, C, and D, these functions, in all probability, must be disturbed considerably by injury to its parenchyma If bile is diverted from the intestinal tract by an external

fistula or by mechanical obstruction of the common duct, the adsorption of vitamins also is affected adversely. No doubt, the reduced production of bile acids which is so apparent in experimental hepatic injury and which probably occurs with clinical hepatic disease, has a similar effect but it is less marked than that caused by diversion of bile. Greaves and Schmidt^{5, 6} have shown that, in the presence of experimental biliary fistula, vitamins B and E as well as certain substances necessary for coagulation of the blood, are not absorbed. Heymann⁷ has demonstrated similarly a failure to absorb vitamin D in the presence of biliary obstruction and also has found that very large doses of this vitamin are necessary to maintain rachitic rats poisoned by carbon tetrachloride. Difficulties in the absorption, storage, and utilization of vitamins thus may be an element of great importance in the progression of hepatic disease. Eppinger⁸ has recognized these difficulties of absorption and has recommended that vitamins be administered only by injection under these circumstances. Possibly with large dosage and the judicious use of bile or bile salts, this may not be necessary but, in any case, the addition of concentrates of vitamins to the diet seems essential.

SPECIFIC SUBSTANCES WHICH MAY PROTECT THE LIVER

It has been assumed that one effect of the forced administration of a high intake of carbohydrate is reduction of the content of fat of the diseased liver, at the same time favoring the deposition of glycogen. This appears to have been accomplished among experimental animals but it is difficult to prove that such a reciprocal relation is demonstrable among human subjects. Various special measures have been advocated to assist in reducing the content of fat of the liver and, on the basis of the well known observations of Allan and his coworkers,⁹ and of Best and others^{10, 11} on pancreatectomized dogs, derivatives of lecithin and choline have been advocated as essential additions to the diet in treatment. The hormone "lipocain" which Dragstedt and his coworkers¹² have isolated from the pancreas, has also been shown experimentally to exert a definite effect on the content of fat of the liver after pancreatectomy. Comfort and I¹³ have shown definite clinical effects among certain patients who had pancreatic atrophy and, presumably, fatty livers from the use of this substance, notably the disappearance of ascites and edema and reduction in the size of the liver. Its use among patients who have fatty metamorphosis of the liver from other causes has been hardly more than considered but there is a theoretical basis for believing that it may be effective.

The recent studies of Neale and his collaborators¹⁴⁻¹⁷ on the effect of various purine derivatives in protecting the liver against experimental injury have attracted much deserved attention. These investigators have shown that sodium xanthine and xanthine, both in the naturally occurring and synthetic forms, will protect the liver of animals against lethal doses of carbon tetrachloride or chloroform. Unfortunately, no definite effect has

been observed in these animals if the purine derivatives are given after the hepatotoxic agent has been administered. Clinical studies have not been reported as yet but certainly the subject holds much promise for further study. It is of interest to note that patients with gout, who may have difficulty in metabolizing the xanthine bases, rarely develop liver atrophy from cinchophen, perhaps the retained xanthine derivatives may exert their protective influence in such cases.

THE NATURE OF HEPATIC INSUFFICIENCY

Various circumstances which may arise in the course of parenchymatous injury of the liver obviously require special therapeutic measures. Of these, the most serious is hepatic insufficiency. Like its counterpart, the uremic state, its nature is not well understood. It differs widely from the syndrome produced by total hepatectomy, hypoglycemia is rare, although it is possible to show minor disturbances of carbohydrate metabolism by appropriate functional tests. It has been possible, in a few instances, to demonstrate some failure in deamination and, rarely, an elevated concentration of uric acid in the blood has been noted. Fatty change in the liver, often a feature of acute forms of atrophy of the liver, may be suggested by a very high concentration of fats in the blood, more frequently, however, the lipid substances of the blood may decrease to low levels and the cholesterol esters may virtually disappear.¹⁸ The excretory functions, particularly in respect to dyes and bilirubin, always are impaired, but this fact may not be as significant as first was supposed. None of the disturbances in metabolism mentioned above are necessarily serious or fatal, in other words, we must look elsewhere for the mechanism by which hepatic failure causes death. The clinical syndrome itself often suggests acute intoxication and it has been suggested that perhaps hepatic insufficiency represents failure of normal processes of detoxification.¹⁹ The liver is probably the first line of defense against many endogenous and exogenous toxins, when its functions in this respect fail, the load falls on the kidneys with resulting renal insufficiency. Although complete proof of this hypothesis is lacking it is justifiable, tentatively to assume that the syndrome of "hepatic insufficiency" is fundamentally dependent on a failure of the mechanism of detoxification.

The known chemical changes of the blood in cases of experimental and clinical hepatic insufficiency may be stated briefly. Soffer and his collaborators²⁰ studying dogs poisoned with large doses of arsphenamine, have found a consistent hemoconcentration among these animals, with an associated fall in the concentration of chlorides of the plasma, the development of acidosis, and an increased content of lactic acid in the blood. Chemical changes in the blood of the degree described are seen very rarely among human subjects, although some concentration of the blood and hypochloremia may occur in the occasional case. The reason for this disturbance in the

metabolism of the chloride is not clear, Beckmann²¹ has suggested that the liver may retain chloride in the capacity of a storage reservoir. The possibility of the liver exerting some hormonal influence on chlorides also has been considered.²² Elevation of the concentration of urea of the blood and nonprotein nitrogen are late developments and, presumably, depend on renal failure rather than on primary hepatic insufficiency. Acidosis, as shown by low carbon dioxide combining power and even by changes in the pH of serum has been observed clinically and elevation of the concentration of lactic acid of the blood comparable to that encountered among Soffer's animals also has been noted.²³ Gautier and his collaborators²⁴ have described an almost identical change in the blood chemistry of a human subject accidentally poisoned with carbon tetrachloride. Anoxemia²⁵ also has been described, a phenomenon which may be of some importance. McMichael²⁶ and others^{27, 28} have demonstrated the sensitivity of the liver to oxygen lack and its rather peculiar vulnerability in this respect because of its unusual blood supply. The nature of the anoxemia in hepatic disease has been discussed by Keys and me²⁹, it appears to depend on a decrease in affinity of hemoglobin for oxygen as shown by displacement of the oxygen dissociation curve to the right. Whether this can be attributed to some fundamental peculiarity of the hemoglobin or to the admixture of other substances in the blood interfering with normal respiration as yet is undetermined.

TREATMENT OF HEPATIC INSUFFICIENCY

Management of hepatic insufficiency depends primarily on the maintenance of an adequate intake of carbohydrate, the administration of sufficient quantities of fluid to dilute and to eliminate toxins, and the correction of hypoglycemia, anoxemia or hemoconcentration, if these happen to be features of the case under consideration. The intake of carbohydrate, as a rule, can be maintained in such cases only by the persistent daily intravenous administration of glucose. Experimentally, Althausen and Stockholm³⁰ have been able to demonstrate that little glycogen is formed by the liver after intravenous administration of glucose when lethal intoxication is present but, in the presence of sublethal intoxication formation of glycogen proceeds at a more satisfactory rate when glucose is given by vein than when equal amounts are given by mouth.

Glucose therapy, although not spectacular, is extremely valuable, Jones'³¹ figures indicate that among individuals who have hepatic insufficiency and who have received glucose intravenously for a period of ten days or longer, the mortality rate is only 22 per cent. In view of the fact that hepatic insufficiency has been regarded as an almost invariably fatal condition, these results are most encouraging. The amount of glucose to be administered depends on whether or not the patient is able to take food by mouth. From 1 to 3 liters of a solution of 5 to 10 per cent glucose can and should be ad-

ministered daily and in some cases even larger amounts have been given by continuous venoclysis

So far as other abnormal chemical conditions of the blood are concerned, hemoconcentration usually is corrected by administration of fluids in the manner described. If the chlorides of the plasma are low in concentration it is a relatively simple matter to administer additional sodium chloride along with the glucose. There are, however, cases in which administration in this manner has had little effect on the level of chloride present in the blood. In one such case recently observed, the use of suprarenal cortical hormone, which is known to produce retention of salt even when no suprarenal cortical insufficiency is present,^{32, 33} brought the concentration of chlorides of the blood up to normal. It is important to maintain the concentration of hemoglobin at a normal level so far as possible, a matter which may require repeated small transfusions. Correction of the anoxemia is assisted materially by such transfusions, both the oxygen capacity and the percentage of oxygen saturation of hemoglobin in arterial blood being definitely elevated by the addition of normal blood.³⁴ In the exceptional case associated with marked cyanosis and hyperpnea, oxygen therapy in some form may be valuable.

TREATMENT OF ASCITES AND EDEMA

The presence of these complications in so many instances of chronic atrophy (cirrhosis) of the liver has attracted attention since the time of Laennec and treatment often has been concentrated on the ascites to the detriment of the patient. Treatment with diuretics and purges has been favored especially in the past and, in fact, the methods employed often have been essentially those used in the treatment of cardiac decompensation. This preoccupation with the problem of transudation becomes justifiable if the disability produced by such conditions is considered and if it is realized that the disappearance of ascites is often synchronous with improvement.

Considerable data have been accumulated recently on the mechanics of transudation associated with hepatic disease which have changed the therapeutic approach to the problem to a great extent. Stasis in the portal venous system formerly has been held to be the principal factor in the formation of ascites, although experimental evidence to substantiate this view has been lacking. Actually, portal venous pressures never have been measured directly, although on anatomic grounds alone, it is reasonable to suppose that portal venous hypertension exists in the presence of a cirrhotic liver. The best available estimations of such pressures are those of Thompson and his collaborators³⁵ and McIndoe.³⁶ The investigators first mentioned, measured pressures directly in the splenic vein in the presence of Banti's disease and in one case of schistosomiasis and splenomegaly, the averages for both cases were about 375 mm of water. McIndoe perfused cirrhotic livers removed at necropsy and found that a pressure of 20 to 30

mm of mercury (260 to 390 mm water) was required to force fluid through the portal venous bed. These represent large increases because normal portal vein pressures probably do not exceed 125 mm of water. Such elevated pressures existing in the portal venous system, of course are to be balanced against the colloidal osmotic pressure exerted by the proteins of the serum. It has been assumed that the colloidal osmotic pressure is reduced in patients who have cirrhosis, by virtue of the hypoproteinemia and reversed albumin-globulin ratio which seem to characterize this condition. The reasons for this disturbance in concentration of the proteins of the plasma have been discussed elsewhere^{25, 37} and will not be considered here. The extent of this reduction of colloidal osmotic pressure dependent on hypoproteinemia has been computed from various formulas but its actual magnitude has not been appreciated until relatively recently. Recent figures³⁸ indicate that, in the presence of chronic injury of the liver, the colloidal osmotic pressure of the serum may be reduced as much as 50 per cent from a normal level of about 372 mm of water. This rather remarkable decrease cannot be correlated satisfactorily with values for total protein although there is much better correlation with figures for serum albumin. In cases of cirrhosis, therefore, the usual balance between hydrostatic pressure in the portal venous system and colloidal osmotic pressure of the serum is greatly disturbed in a direction which favors transudation.

Such simple pressure relationships, however, probably are not the only factors in the problem, a third variable must be considered. It has been assumed for years that some injury to serosal surfaces may exist in cases of hepatic disease, in fact Eppinger has spoken of "Serosc Entzündung" with increased permeability of such surfaces as the pleura and peritoneum. Among animals whose livers have been rendered cirrhotic by carbon tetrachloride and which have been subjected further to plasmapheresis in order to reduce the concentration of proteins of the plasma, Bollman³⁹ has found no evidence of a constant "edema level" as measured by determining osmotic pressures. Both observations, of course, argue for the existence of a third factor, that of increased permeability of capillaries and membranes. It is suggested that the "permeability vitamin" recently isolated by Szent-Gyorgyi⁴⁰ may be the determining factor in our equation. This material, a flavone glucoside, is present in citrus fruits and is allied closely to vitamin C, if it is stored in the same manner as vitamin C, it is reasonable to suppose that it may be affected by pathologic change in the liver.

On the basis of the above-mentioned evidence the logical treatment of ascites and edema, therefore, would be directed toward (1) improvement of the condition of the liver, a matter which has been discussed, (2) decrease of portal venous pressure, and (3) elevation of the concentration of proteins of the plasma thereby increasing the colloidal osmotic pressure of the serum. The first requirement can be met only by some surgical procedure, of which the Talma-Morison omentopexy is a fair example. General surgical experience, as cited by various authorities,⁴¹⁻⁴³ has been

somewhat disappointing with this procedure and it cannot be recommended wholeheartedly. The heroic process of partial enterectomy as performed by Fuller and her collaborators⁴⁴ may serve its purpose by reduction of portal venous flow, but, possibly, reduction of the area of serous surface through which transudation can occur is equally important.

Attempts to elevate the concentration of proteins in the plasma offer a considerably greater prospect of success than omentopexy or partial enterectomy. Centurion⁴⁵ attempted to accomplish this by reinjecting ascitic fluid and, by virtue of the content of albumin of this material, occasionally achieved the desired effect. Route's operation,⁴⁶ that of permanently draining the ascitic fluid into the proximal end of the saphenous vein (venoperitoneostomy) has been employed with reported good results. Both of these rather formidable measures obviously should be deferred until an attempt has been made to elevate the osmotic pressure of the patient's serum by less spectacular means. For obvious reasons, a relatively high dietary intake of protein is believed to be desirable. Transfusions of whole blood and plasma have a temporarily beneficial effect because of the additional normal albumin which they supply. The use of substitutes for blood such as solution of acacia also has been tried with somewhat encouraging results, as Kerkhof,⁴⁷ and Butt and Keys⁴⁸ recently have shown, concentrated solution of acacia raises the osmotic pressure of serum *in vitro* and *in vivo* and, in some instances, has produced diuresis among patients who have hypoproteinemia. Similar effects, but on a smaller scale, have been noted among patients who have hepatic disease. An injection of 500 c.c. of a solution of 6 per cent acacia on three consecutive days frequently will produce a temporary rise in osmotic pressure of approximately 20 per cent, a change sufficiently great to retard the rate of accumulation of fluid. Large doses must be used with caution since they may produce hepatic damage and depress the total protein still further. Acacia, of course, is eliminated slowly from the blood stream and it is sometimes necessary to repeat its administration to secure the desired effect.

In addition to the measures mentioned above the effect of vitamins on the proteins of the plasma may be considered. Field⁴⁹ has produced evidence to show that vitamin B complex given parenterally in large doses may elevate the concentration of proteins of the plasma and retard transudation even when such a rise in concentration is not large. Patek⁵⁰ has recommended independently a combined attack with all available concentrates of vitamins, he advises that the patients be given, daily in addition to the diet mentioned in an earlier paragraph, 30 minims of *Oleum Percomorphum*, 12 ounces of orange juice, 2 ounces of Valentine's Liver Extract, 3 drams of Vegex and parenteral crystalline vitamin B₁, the latter being intravenously injected daily in doses varying between 4 and 10 mg. His results in a selected group of cases have been very encouraging. The practice of feeding of concentrates of vitamins together with a diet high in carbohydrate and protein to patients who have cirrhosis has been followed at The Mayo Clinic

for some months and strikingly good responses have been noted in some cases. As has been stated, patients who are able to eat a liberal diet invariably make better progress than those who have anorexia and, certainly, attempts at forced feeding and the use of concentrates of vitamins have much to recommend them on this basis alone.

Intramuscular injections of liver extract may also have some direct effect on nitrogen balance and on the retention of protein. In cases of pernicious anemia, the use of liver extract will produce a positive nitrogen balance⁵¹ and, apparently it has somewhat the same effect in cases of hepatic disease although on a much smaller scale. As Heath and Taylor⁵² have shown, hemoglobin is formed first in response to the stimulation of liver fractions and this formation may continue even at the expense of the protein of the plasma and tissues. If the patient's dietary intake of nitrogen is sufficiently large, more nitrogen may be retained and, under such circumstances, it is conceivable that a rise in the concentration of protein of the plasma might occur. Studies on the metabolism of nitrogen in cases of liver disease, when made on edematous patients who had capricious appetites, are difficult to interpret but, in at least two instances, evidence has been obtained which indicates a strongly positive nitrogen balance after administration of large doses of liver extract parenterally. In these experiments, elevation of the concentration of proteins of the plasma was not sufficiently great to be worthy of comment but there appeared to be definite clinical improvement and a reduction in the rate of transudation.

The use of mixtures of amino acids intravenously eventually may help to solve the problem of hypoproteinemia. Elman^{53, 54} has shown that a mixture of amino acids obtained from hydrolyzed casein, fortified with cystine and tryptophane, has produced definite retention of nitrogen among dogs after plasmapheresis. Further therapeutic tests with mixtures of amino acids among patients who have hypoproteinemia must be performed before any definite statements can be made as to the efficacy of amino acids in treatment.

In concluding this discussion of ascites and edema, some reference to the time-honored use of diuretics is essential. The acid-producing salts and the mercurial diuretics which were in vogue ten years ago are less popular today, because a striking diuretic response appears to be difficult to obtain among a majority of patients who have damaged livers. Diuretics may be ineffective early in the course of treatment and produce good results later when the patient's general condition (and presumably the state of the parenchyma of the liver) has improved. Diuretic treatment, however, never should be forced, trial of potassium or ammonium salts for a few days followed by one or more doses of the injectible mercurial diuretics should be sufficient to determine whether or not the patient in question will respond favorably. If a good increase in the volume of urine is not obtained by this means, diuretics should be omitted, forced administration has been known, on many occasions, to lead to the development of fatal hepatic and renal insufficiency.

Tapping entails far less risk and, as Osler^{55, 56} noted, may be resorted to frequently without greatly affecting the general condition of the patient. White's⁵⁷ frequently quoted observations on the usual fatal termination of portal cirrhosis after tapping, certainly do not hold at the present time.

THE ANEMIA OF LIVER DISEASE

Macrocytic anemia which is a frequent finding in all instances of advanced or chronic hepatic injury⁵⁸ is not particularly responsive to treatment. The anemia itself is supposedly dependent on failure of the liver to store the active hematopoietic principle or on its inability to present it to the body in a proper form for utilization.⁵⁹ This difficulty in utilization is apparently of considerable importance, because long-continued and persistent treatment with large dosages of active fractions of liver is required to produce any particular effect on the blood. Frequent transfusions and the intermittent administration of iron in some form are necessary adjuvants to treatment, particularly in the seriously ill patient whose intake of food is limited.

HEMORRHAGE IN LIVER DISEASE

Hemorrhage associated with disease of the liver may assume two distinct forms: (1) that which results from rupture of collateral circulatory channels, and (2) that which is dependent on some intrinsic change in the coagulating properties of the blood. The control of the first situation, which ordinarily is represented by bleeding from esophageal varices, should be regarded as a surgical problem. Splenectomy is helpful in the treatment of hemorrhage which characterizes Banti's disease, achieving its effects partly by the reduction of the circulatory load on the portal system and partly because the operation cuts off one large contributing source of blood to the esophageal varices coming through the *vasa brevia* of the spleen. Unfortunately, the procedure is not feasible in most instances of primary cirrhosis because of the risk involved. Direct ligation of the coronary veins of the stomach⁶⁰ has been attempted as a means of controlling bleeding from collateral channels, although it is technically difficult and is subject to certain definite limitations, it may be considered in certain cases after ordinary palliative measures have failed.

So-called "cholemic" bleeding has been, for years, an unsolved problem. The nature of the coagulation defect has been, until lately, an unsettled question and methods of treatment have been largely empirical. Deficiencies of calcium have been postulated and, also, it has been suggested that various sulphydryl⁶¹ anticoagulants may be present in jaundiced blood. The most recent evidence on the subject indicates that neither of these theories is correct. Quick⁶² was the first to note that the deficiency was probably of the prothrombin of the blood, all other elements necessary for coagulation being present in normal amounts. This observation has been

corroborated by numerous workers and it may be regarded as an established fact

A good deal of further information about deficiency of prothrombin has been forthcoming in recent months and has revealed the existence of three widely varied conditions associated with such a shortage. Hawkins and Brinkhous,⁶³ in studying the hemorrhagic state induced by complete biliary fistula in dogs, have noted a deficiency of prothrombin and showed that it could be corrected by the feeding of bile. Apparently, therefore, one factor necessary for the maintenance of a normal level of prothrombin is the presence of bile in the bowel.

A second factor was pointed out much earlier by the pioneer studies of Dam and his coworkers⁶⁴⁻⁶⁸. They demonstrated that internal, subcutaneous, and intramuscular hemorrhages developed among chicks fed on a diet deficient in certain fat soluble compounds, but adequate in respect to vitamins A, B₁, B₂, C and D and total fat and cholesterol. This bleeding is associated with, and apparently is attributable to, a decrease in the concentration of prothrombin of the blood. The hemorrhagic tendency, as Dam⁶⁶ first showed, is cured promptly by administering a substance found in the unsaponifiable, nonsterol fraction of hog-liver fat and in alfalfa. This is the substance which has been designated tentatively as vitamin K (Koagulations-Vitamin).

Thus, there are two factors, the presence of bile in the bowel and a hypothetical fat soluble vitamin, which are known to be of importance in maintaining a normal level of prothrombin. A third and equally important factor remains to be considered. A marked hemorrhagic tendency exists among animals fed spoiled sweet clover hay and, as Roderick⁶⁹ and later, Quick⁶² showed, this also depends on a deficiency in prothrombin. The condition is relieved by transfusion of blood and by feeding alfalfa, which is protective in concentrations as low as 5 per cent of the total diet. Quick concluded that some toxic factor present in spoiled sweet clover hay depleted the supply of prothrombin and that an exogenous supply of some unknown material was required for its repletion. Just how spoiled sweet clover affects the normal store of prothrombin is not known. Possibly the parenchyma of the liver is affected since Roderick⁷⁰ demonstrated focal necrosis of the liver in some animals dying from toxic sweet clover disease. This possibility is supported by the recently published studies of Warner, Brinkhous and Smith⁷¹ who showed that, in cases of experimental chloroform intoxication, a deficiency in both fibrinogen and prothrombin occurred. By varying the dose of chloroform, deficiency in prothrombin alone could be produced and the fibrinogen was left virtually unaltered. Their data appeared to indicate that the liver is concerned in the manufacture of prothrombin. It seems justifiable then, to conclude that 1. The hemorrhagic state associated with disease of the liver is attributable to a deficiency of prothrombin which, in turn, is attributable to failure of absorption or utilization of some substance normally present in the diet which required bile for

its absorption 2 This substance may be the hypothetical coagulation vitamin (vitamin K) 3 Additional "toxic" factors may deplete the supply of prothrombin, as occurs in cases of sweet clover disease and necrosis of the liver caused by chloroform

From a clinical standpoint, administration of extracts containing vitamin K together with bile or bile salts to patients who have jaundice has rapidly reduced an elevated prothrombin time to a point within normal limits and, in certain cases, has prevented hemorrhage or has had a definite inhibitory effect on actual bleeding Administration of bile alone to an individual who was ingesting an adequate diet has resulted in a shortening of the increased prothrombin time Administration of vitamin K alone, when bile is absent from the intestinal tract, has had little or no effect in decreasing the elevated prothrombin time of one individual

The results obtained thus far encourage the belief that prevention and control of the hemorrhagic diathesis among patients who have obstructive jaundice or primary injury of the liver may be accomplished by administration of bile and concentrates of vitamin K Warner, Brinkhous and Smith at the University of Iowa have obtained independently results which confirm this impression

The application of some of these methods of treatment to specific cases may be illustrated best by a brief report of two cases The first pertains to the management of a case of hepatic insufficiency associated with the ascitic stage of cirrhosis, the second, to the problem of cholemic bleeding

CASE REPORTS

Case 1 A man, aged 47 years, was admitted to the hospital, giving a history of jaundice, ascites, and edema of six weeks' duration There was a long history of alcoholism, and hepatic enlargement had been noted by the patient's physician more than a year previous to admission here Prior to the development of icterus he had lost some weight and had bled from the nose and gums On physical examination, the striking findings were slight cyanosis, jaundice, anasarca, and malnutrition, there was some glossitis and the breath had a "mousy" odor The size of the liver and spleen could not be determined because of the large amount of fluid present in the abdomen Laboratory studies revealed marked macrocytic anemia, the concentration of bilirubin was 3 mg per 100 cc of serum, and retention of bromsulphalein was present grade 3 (on a basis of 1 to 4), the total concentration of proteins of the plasma was normal (67 gm) but the albumin-globulin ratio was 0.45 and the colloidal osmotic pressure was 200 mm of water The clinical diagnosis was portal cirrhosis with impending hepatic insufficiency

Paracentesis was performed two days, 10 days, and one month after admission, respectively and two small transfusions (250 cc) were given in the first month the patient was in the hospital Because of an inadequate intake of food, glucose was given intravenously (1 liter of a 10 per cent solution) daily for five weeks

* Since this paper was written a personal communication from Dam and Glavind has been received They have published preliminary reports (Vitamin K I Den Menneskelige Patologie Saertryk af Ugeskrift for Laeger, No 10 pp 248-255, 1938, and Vitamin K in human pathology, Lancet, 1938, ccxlv, 720-721) which are in agreement with the hypothesis of prothrombin deficiency as a cause for hemorrhage in jaundiced patients They have also prepared an emulsion of spinach, containing vitamin K which reduces the coagulation time of blood on intramuscular injection

Brewers' yeast, iron, and cevitic acid were given in full doses. Diuretics were tried cautiously and proved ineffective. One month after admission, 1500 cc of a solution of 6 per cent acacia was given in three equal and divided doses on successive days, the colloidal osmotic pressure rose about 30 mm of water and gradually fell off, some increase in the output of urine was apparent and the rate of accumulation of fluid was never such as to require tapping thereafter. At about this time, intramuscular injections of liver extract were begun and 25 doses (1 cc each) of a concentrated preparation was given in the next six weeks, the anemia was corrected very slowly and neither the concentration of proteins of the plasma nor the osmotic pressure of the serum was affected greatly. Three transfusions of blood (500 cc each) also were given in this period. In spite of the apparent lack of improvement in the concentration of the proteins of the blood, the appetite gradually increased and the ascites and edema slowly disappeared. Eighty-four days after admission the patient was dismissed free of jaundice and anasarca, with a virtually normal number of erythrocytes. The liver and spleen were just palpable but retention of dye persisted. His physician at home reported that the patient was well and in good condition six months later and there had been no recurrence of his symptoms after one year.

In reviewing this patient's clinical course the most remarkable feature was the very gradual improvement with almost complete lack of any periods of spectacular improvement. The lesson to be learned is, of course, that persistence may accomplish much in the rehabilitation of these patients and that eventual recovery depends on restoration of normal hepatic function rather than on elimination of any one feature of the syndrome associated with this disease. Obviously, this is a slow process, but the results, once attained, are eminently satisfactory. We have records of several similar cases, some of which were not attributable to the use of alcohol or other hepatotoxins.

Case 2 The control of bleeding presents a somewhat more dramatic situation, one in which prophylaxis is to be preferred to curative treatment. A man, aged 51 years, had cholecystgastrostomy performed for obstructive jaundice caused by cancer of the head of the pancreas following four days of preparation with glucose intravenously. Vitamin K and bile salts were given for one day only before operation, because the Quick prothrombin time and the Lee coagulation time had been reported as normal on two occasions. It was noted by the surgeon at operation that the liver was pale green in color and that no bile had been reaching the intestine. Immediately following operation, the prothrombin coagulation time rose from a normal level of 20 seconds to 30 seconds and then to 70 seconds, on the third postoperative day, signs of internal hemorrhage were apparent. By the time the latter report was received and before more vitamin K and bile salts could be administered, profuse bleeding occurred from the gastrointestinal tract. The concentration of hemoglobin fell to 4.9 gm per 100 cc of blood and the patient lost consciousness. A single transfusion of 500 cc of blood had little effect on the prothrombin time as measured some six hours later. After 2 cc of an extract of vitamin K and 250 cc of bile had been administered by a duodenal tube on two successive days, the prothrombin time fell to a point within normal limits (20 seconds) and signs of active bleeding ceased. The same treatment in smaller dosage was continued daily thereafter and no further bleeding occurred.

The above experience has been duplicated in other instances and is by no means a special circumstance. Present difficulties are centered chiefly about

the detection of prospective "bleeders" and the delivery of vitamin K and bile into the intestinal tracts of patients who have active bleeding. Both are technical problems and, doubtless will be overcome, the important consideration is that in cases of both obstructive jaundice and parenchymatous hepatic injury the administration of bile and a vitamin-like material reduces the prothrombin time of blood to a point within normal limits and thereby controls or prevents active bleeding.

SUMMARY

The principal requirements in the treatment of parenchymatous hepatic disease appear to be the maintenance of optimal conditions to allow for regeneration and repair of the parenchyma of the liver.

The use of special diets high in carbohydrate, vitamin concentrates, and liver extract parenterally are valuable in this connection. The treatment of hepatic insufficiency depends chiefly on the maintenance of a high intake of fluid with ample supplies of glucose, no specific protective substances, as yet, have been applied successfully to the treatment of this condition. The hemorrhagic diathesis associated with chronic hepatic disease and jaundice is dependent, in part, on deficient absorption of substances necessary for coagulation of the blood and, in particular, on depletion of the prothrombin of the blood because of hepatic injury. The use of bile, bile salts, and vitamin K in treating this condition has been discussed.

REFERENCES

- 1 BOYCE, F. F., VEAL, J. R., and MCFETRIDGE, E. M. An analysis of the mortality of gall-bladder surgery with a special note on the so-called liver death based on 404 consecutive surgical cases and 100 consecutive surgical deaths in the New Orleans Charity Hospital, Surg., Gynec. and Obst., 1936, **LXIII**, 43-53.
- 2 LEGG, WICKHAM. On cirrhosis of the liver, St Bartholomew's Hosp. Rep., 1872, **viii**, 74-83.
- 3 MANN, F. C., FISHBACK, F. C., GAY, J. G., and GREENE, G. F. Experimental pathology of the liver. Studies III, IV, and V, Arch. Pathol., 1931, **xii**, 787-793.
- 4 OPIE, E. L., and ALFORD, L. B. The influence of diet upon necrosis caused by hepatic and renal poisons. Part 1. Diet and the hepatic lesions of chloroform, phosphorus or alcohol, Jr. Exper. Med., 1915, **xxi**, 1-20.
- 5 GREAVES, J. D., and SCHMIDT, C. L. A. The nature of the factor concerned in loss of blood coagulability of bile fistula rats, Proc. Soc. Exper. Biol. and Med., 1937, **xxxvii**, 43-45.
- 6 GREAVES, J. D., and SCHMIDT, C. L. A. Relation of bile to absorption of vitamin E in the rat, Proc. Soc. Exper. Biol. and Med., 1937, **xxxvii**, 40-42.
- 7 HEYMANN, WALTER. Importance of the liver for the antirachitic efficacy of vitamin D, Proc. Soc. Exper. Biol. and Med., 1937, **xxxvi**, 812-814.
- 8 EPPINGER, HANS. Die Leberkrankheiten, allgemeine und spezielle Pathologie und Therapie der Leber, 1937, Julius Springer, Vienna, 801 pp.
- 9 ALLAN, F. N., BOWIE, D. J., MACLEOD, J. J. R., and ROBINSON, W. L. Behaviour of depancreatized dogs kept alive with insulin, Brit. Jr. Exper. Pathol., 1924, **v**, 75-83.
- 10 BEST, C. H., and HERSHEY, J. M. Further observations on the effects of some component of crude lecithine on depancreatized animals, Jr. Physiol., 1932, **LXXV**, 49-55.

- 11 BEST, C H, FERGUSON, G C, and HERSHEY, J M Choline and liver fat in diabetic dogs, *Jr Physiol*, 1933, lxxix, 94-102
- 12 DRAGSTEDT, L R, VAN PROHASKA, J, and HARMS, H P Observations on a substance in pancreas (a fat metabolizing hormone) which permits survival and prevents liver changes in depancreatized dogs, *Am Jr Physiol*, 1936, cxvii, 175-181
- 13 SNELL, A M, and COMFORT, M W Hepatic lesions presumably secondary to pancreatic lithiasis and atrophy, report of two cases, *Am Jr Digest Dis and Nutr*, 1937, iv, 215-218
- 14 NEALE, R C The protective action of certain purines against liver necrosis produced by carbon tetrachloride and chloroform, *Science*, 1937, lxxxi, 83-84
- 15 NEALE, R C, and WINTER, H C The identification of the active crystalline substance from liver which protects against liver damage due to chloroform or carbon tetrachloride, and a study of related compounds, *Jr Pharmacol and Exper Therap*, 1938, lxi, 127-148
- 16 FORBES, J C, and NEALE, R C A new preparation protecting against rat liver necrosis, *Proc Soc Exper Biol and Med*, 1936, xliii, 319-322
- 17 FORBES, J C, and McCONNELL, J S Crystallization of liver fraction protecting against necrosis from carbon tetrachloride or chloroform administration, *Proc Soc Exper Biol and Med*, 1937, lxxvi, 359-360
- 18 EPSTEIN, E Z, and GREENSPAN, E B Clinical significance of the cholesterol partition of the blood plasma in hepatic and in biliary diseases, *Arch Int Med*, 1936, lvi, 860-890
- 19 BOLLMAN, J L, and MANN, F C The physiology of the impaired liver, *Ergebn d Physiol*, 1936, xxxviii, 445-492
- 20 SOFFER, L J, DANTES, D A, and SOBOTKA, H Electrolytes of blood and urine of dogs with acute hepatic injury produced by arsphenamine, *Arch Int Med*, 1937, lxv, 509-521
- 21 BECKMANN, K Leber und Mineralhaushalt, *Klin Wchnschr*, 1930, ix, 49-51
- 22 PICK, E P Wasser- und Mineralstoffwechsel in ihren Beziehungen zu Verdauungs- und Stoffwechselkrankheiten, *Verhandl d Gesellsch f Verdauungs- u Stoffwechselkrankh*, 1925-1926, v-vi, 125-136
- 23 SNELL, A M, and ROTH, G M The lactic acid of the blood in hepatic disease, *Jr Clin Invest*, 1932, xi, 957-971
- 24 GAUTIER, C, CHATRON, M, and SEIDMANN, P Intoxication par le tetrachlorure de carbone, hyperazotemie elevee, effondrement de la reserve alcaline, hypochloremie considerable Alcalinisation et rechloruration, *Bull et mem Soc med d hop de Par*, 1933, xlii, 1638-1650
- 25 SNELL, A M, and MACLAY, E The effects of chronic diseases of the liver on the composition and physicochemical properties of blood, changes in the serum proteins, reduction in the oxygen saturation of arterial blood, *ANN INT MED*, 1935, ix, 690-711
- 26 McMICHAEL, J The oxygen supply of the liver, *Quart Jr Exper Physiol*, 1937, xxi, 73-87
- 27 CAMPBELL, J A Concerning the problem of Mount Everest, *Lancet*, 1928, ii, 84-86
- 28 ROSIN, A Morphologische Organveränderungen beim Leben unter Luftverdünnung, *Beitr z path Anat u z allg Path*, 1928, lxxx, 622-639
- 29 KEYS, A, and SNELL, A M Respiratory properties of arterial blood in normal man and in patients with disease of the liver position of the oxygen dissociation curve, *Jr Clin Invest*, 1938, xvi, 59-67
- 30 ALTHAUSEN, T A, and STOCKHOLM, M Deposition of glycogen in normal and in experimentally damaged livers after oral and intravenous administration of dextrose, *Trans Am Gastro-Enterol Assoc*, pp 106-110, 1937
- 31 JONES, C M The treatment of acute hepatic insufficiency and its relation to prognosis, *Am Jr Digest Dis and Nutr*, 1936, iii, 624-629

- 32 HARROP, G A, and THORN, G W Studies on the suprarenal cortex VI The effect of suprarenal cortical hormone upon the electrolyte excretion of the normal intact dog A proposed method of comparative assay, *Jr Exper Med*, 1937, lxxv, 757-766
- 33 THORN, G W Effect of adrenal cortical hormone on renal excretion of electrolytes in normal subjects, *Proc Soc Exper Biol and Med*, 1937, xlxvi, 361-364
- 34 JUDD, E S, SNELL, A M, and HOERNER, M T Transfusion for jaundiced patients, *Jr Am Med Assoc*, 1935, cv, 1653-1658
- 35 THOMPSON, W P, CAUGHEY, J L, WHIPPLE, A O, and ROUSSELOT, L M Splenic vein pressure in congestive splenomegaly (Banti's syndrome), *Jr Clin Invest*, 1937, xvi, 571-572
- 36 MCINDOE, A H The vascular lesions of portal cirrhosis, *Arch Pathol and Lab Med*, 1928, v, 23-42
- 37 MYERS, W K, and KEEFER, C S Relation of plasma proteins to ascites and edema in cirrhosis of the liver, *Arch Int Med*, 1935, lv, 349-359
- 38 BUTT, H R, and KEYS, A Colloid osmotic pressure studies of normal individuals and of those with hypoproteinemia, *Proc Staff Meet Mayo Clinic*, 1937, xii, 566-571
- 39 BOLLMAN, J L Unpublished data
- 40 SZENT-GYORGYI, A *Verhandl d Gesellschaft f Verdauungs- u Stoffwechselkrankh*, 1934, xii, 49-57
- 41 HOPFNER, E *Der Aszites und seine chirurgische Behandlung*, *Ergebn d Chir u Orthop*, 1913, vi, 410-480
- 42 HUGHSON, W Portal cirrhosis with ascites and its surgical treatment, *Arch Surg*, 1927, xv, 418-440
- 43 ELIOT, E, and COLP, R The operation of omentopexy in cirrhosis of the liver, *Surg, Gynec and Obst*, 1919, xxviii, 309-315
- 44 FULLER, M K, COOK, D D, MACKENZIE, W O M, and ZBITNOFF, N Enterectomy in the surgical treatment of hepatic cirrhosis or portal obstruction with ascites, *Surg, Gynec and Obst*, 1937, lxxv, 331-335
- 45 CENTURION Personal communication to the author
- 46 MILLER, R T The surgical treatment of ascites Direct drainage of the fluid into the blood stream by implantation of the saphenous vein in the peritoneum, report of five cases, *Pennsylvania Med Jr*, 1915, xiv, 413-420
- 47 KERKHOF, A C Plasma colloid osmotic pressure as a factor in edema formation and edema absorption, *ANN INT MED*, 1937, xi, 867-881
- 48 BUTT, H R, and KEYS, A Osmometric study of gum acacia solutions used for intravenous injection, *Jr Phys Chem*, 1938, xlii, 21-27
- 49 FIELD, H The relation of vitamin B to serum proteins and to edema, *Jr Clin Invest*, 1937, xvi, 663-664
- 50 PATEK, A J, JR Treatment of alcoholic cirrhosis of the liver with high vitamin therapy, *Proc Soc Exper Biol and Med*, 1937, xlxvii, 329-330
- 51 ALT, H L The metabolism in pernicious anemia, *Arch Int Med*, 1929, xliii, 488-503
- 52 HEATH, C W, and TAYLOR, JF H L The nitrogen metabolism in anemia during the regeneration of blood, *Jr Clin Invest*, 1936, xv, 411-418
- 53 ELMAN, R Intravenous injection of aminoacids in regeneration of serum protein following severe experimental hemorrhage, *Proc Soc Exper Biol and Med*, 1937, xlxvi, 867-870
- 54 ELMAN, R Urinary output of nitrogen as influenced by intravenous injection of a mixture of amino-acids, *Proc Soc Exper Biol and Med*, 1938, xlxvii, 610-613
- 55 OSLER, W Recovery in cirrhosis of the liver, *Med News*, Philadelphia, 1888, lii, 47
- 56 OSLER, W Is cirrhosis of the liver curable? *Med News*, Philadelphia, 1886, xliix, 327
- 57 WHITE, W H The cause and prognosis of ascites due to alcoholic cirrhosis of the liver, to perihepatitis, and to chronic peritonitis, *Guy's Hospital Rep*, 1892, xlxiv, 1-42
- 58 FELLINGER, K, and KLIMA, R Untersuchungen uber Anamien bei Leberzirrhosen, *Wien klin Wchnschr*, 1933, xlii, 1191-1194

- 59 GOLDHAMER, S M, ISAACS, R, and STURGIS, C C The role of the liver in hemato-
poiesis, *Am Jr Med Sci*, 1934, clxxviii, 193-199
- 60 ROWNTREE, L G, WALTERS, W, and McINDOE, A H End results of tying off the
coronary vein for the prevention of hemorrhage from esophageal varices, *Proc Staff
Meet Mayo Clinic*, 1929, iv, 263-264
- 61 NAFFZIGER, H C, CARR, J L, and FOOTE, F S Obstructive jaundice the cause and
prevention of the bleeding dyscrasia, *Ann Surg*, 1937, cvi, 745-751
- 62 QUICK, A J The coagulation defect in sweet clover disease and in the hemorrhagic
chick disease of dietary origin a consideration of the source of prothrombin, *Am Jr
Physiol*, 1937, cxviii, 260-271
- 63 HAWKINS, W B, and BRINKHOUS, K M Prothrombin deficiency the cause of bleeding
in bile fistula dogs, *Jr Exper Med*, 1936, lxi, 795-801
- 64 DAM, H Haemorrhages in chicks reared on artificial diets a new deficiency disease,
Nature, 1934, cxxxiii, 909-910
- 65 DAM, H The antihæmorrhagic vitamin of the chick, occurrence and chemical nature,
Nature, 1935, cxxxv, 652-653
- 66 DAM, H The antihæmorrhagic vitamin of the chick, *Biochem Jr*, 1935, xxix, 1273-1285
- 67 DAM, H, SCHØNHEYDER, F, and LIESE, L The requirement for vitamin K of some
different species of animals, *Biochem Jr*, 1937, lxxxi, 22-27
- 68 DAM, H, SCHØNHEYDER, F, and TAGE-HANSEN, E Studies on the mode of action of
vitamin K, *Biochem Jr*, 1936, lxxx, 1075-1079
- 69 RODERICK, L M A problem in the coagulation of the blood sweet clover disease of
cattle, *Am Jr Physiol*, 1931, xcvi, 413-425
- 70 RODERICK, L M The pathology of sweet clover disease in cattle, *Jr Am Vet Med
Assoc*, 1929, lxiv, 314-325
- 71 WARNER, E D, BRINKHOUS, K M, and SMITH, H P Bleeding tendency of obstructive
jaundice prothrombin deficiency and dietary factors, *Proc Soc Exper Biol and Med*,
1938, xlvii, 628-630

CONGENITAL MALFORMATIONS OF THE PULMONIC AND AORTIC VALVES^{*}

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CONGENITAL malformations of the semilunar valves are relatively infrequent and usually consist of a variation in the number of cusps. Acquired malformations are seldom found, but must be carefully distinguished from the congenital form.

Simonds, in 1923, collected 209 records of cases of alteration in the number of cusps. In his paper on this subject, he reported his series together with those of three other investigators, a total of 43 cases discovered in the course of 15,666 postmortem examinations. Abbott, in 1932, in her tabulation of 1000 cases, reported 43 instances in which the defects were unaccompanied by other lesions and a total of 125 in which the anomaly was accompanied by other lesions. Simonds gave a logical explanation of the mechanism involved in the development of these defects.

EMBRYOLOGY

In the developmental division of the common arterial trunk into the aorta and pulmonary artery, two groups of swellings develop on the inner surface of the vessel. The four swellings distally situated with respect to the heart are the *anlagen* of the semilunar cusps, later, by descent and torsion of the vascular trunk, they come to occupy their normal position. The swellings proximally situated are two. Figures 1, 2, and 3, taken from Simonds' work, will suffice to show the normal division and the supposed manner of abnormal division of the arterial trunk.

ETIOLOGY AND TYPES

A pulmonic valve consisting of four cusps is the most frequent malformation. In the majority of cases, there is no evidence of a previous inflammatory process and most likely this type of anomaly is the result of the occurrence of an extra pad or swelling in the common vascular trunk. From this explanation it would seem that four cusps would occur as frequently in the aortic valve as in the pulmonic valve. However, four cusps in the aortic valve are rare. The semilunar cusps are supposedly formed by a hollowing out process. It is probable that an abnormality in this mechanism would result in the formation of two cusps from one pad or swelling. This latter hypothesis does not seem plausible in view of the specimens examined in this series because all the accessory cusps appear as small, interpolated

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structures, well-formed, unattached to the adjacent cusps by adhesions, and approximately half the size of the normal cusps. If the deformity were the result of abnormal hollowing out, one would expect to find two small cusps which together would be equal in size to a single normal cusp.

The same possibilities apply to the anomalous aortic valve, consisting of four cusps. Why this type occurs so infrequently has not been explained satisfactorily.

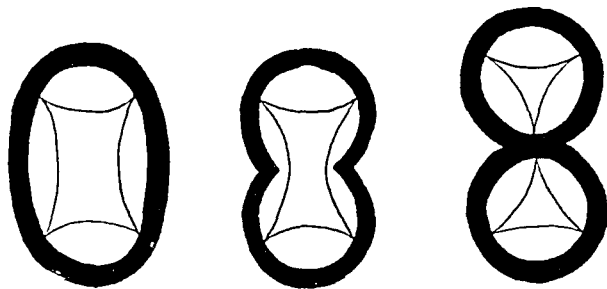


FIG 1 Mechanism of normal division of common trunk into aorta and pulmonary artery with the formation of two sets of tricuspid valves (after Simonds)

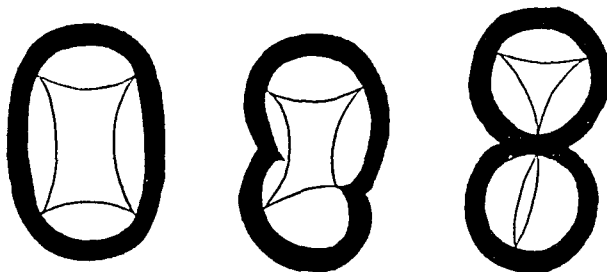


FIG 2 Abnormal division of the common trunk with resulting bicuspid aortic valve (after Simonds)

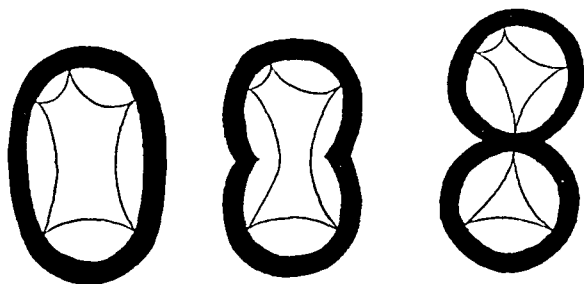


FIG 3 Small interpolated cusp which may be the mechanism in the production of the four-cusp pulmonary valve (after Simonds)

The defects consisting of bicuspid pulmonary and aortic valves may be attributable more frequently to an inflammatory process than to a congenital defect of development such as those described. The bicuspid valve may have cusps of equal or unequal size. Bicuspid aortic valves are the more frequent. Prenatal processes or postnatal inflammatory processes possibly explain these defects. In the latter instance, the condition cannot be considered a congenital malformation. Postnatal deformity frequently is

caused by fusion of two adjacent cusps with a subsequent endocarditis, erosion, and ulceration of the partition, one cusp and one sinus of Valsalva remaining. In the case of a bicuspid aortic valve resulting from such inflammatory change, there is usually a ridge remaining in the middle of the larger cusp, which represents the point of cleavage. This aids in differentiating the congenital and acquired anomalies and has been employed by Bishop and Trubek in their valuable contribution to this subject.

In 1886, Osler, in describing the bicuspid aortic valve, advanced three characteristics of the congenital form which would serve to distinguish it from the acquired form. These are: 1. The free edge is usually straight, without nodular thickening, indicative of a corpus arantii. 2. The attached border presents a normal contour or a shallow groove, indicating the junction of two cusps. 3. The aortic side of the valve presents a more or less distinct raphé or frenum which divides or indicates a division into two sinuses. This raphe varies in position from that of an elevated ridge on the aortic wall to a single or double barred ridge extending a variable distance along the valve.

When marked calcification of the aortic ring and valves is found, the only definite proof of congenital malformation is lack of microscopic evidence of inflammatory change. Bishop and Trubek examined serial sections of the raphé which is present in the lower portion of the larger cusp. The presence or absence of other cardiac anomalies may also be of value in differentiating these conditions. Abbott expressed the opinion that the bicuspid aortic valve has an etiology that differs from that of a similar defect of the pulmonary valve.

CLINICAL DIAGNOSIS

Deformities of the pulmonic and aortic cusps, unless associated with other cardiac anomalies, do not give rise to clinical signs or symptoms, and at present no criteria exist for the diagnosis of these defects.

PROGNOSIS

If uncomplicated, these defects seem to cause no cardiac embarrassment. They are prone to undergo early calcification and are also subject to infectious processes such as subacute bacterial endocarditis. Thus, in spite of their benign clinical manifestation, they may cause death.

The material studied (table 1) fulfills the qualifications stated by Osler for the identification of congenital valvular defects, doubtful cases were not included, and sections were not examined microscopically.

In the 30 cases of alteration in the number of cusps of the pulmonic and aortic valves, the most common abnormality was the pulmonic valve of four cusps. This defect was found in 15 of the 30 cases. In the clinical records of the 15 cases, mention was not made of signs or symptoms that might have led one to suspect the presence of supernumerary valve leaflets. The

TABLE I
Summary of Material Studied

Lesion	Cases
Aortic valve	
2 cusps	9
4 cusps	3
Associated anomalies	5
Pulmonic valve	
2 cusps	3
4 cusps	15
Associated anomalies	2

defect as seen at necropsy consisted usually of a small, well defined cusp approximately half the size of a normal cusp. In two cases of the 15, two small cusps, equal in size, were found, and in both of these, the valves were competent. Four cardiac deaths were recorded, three of hypertensive cardiac disease and one of chronic adhesive pericarditis. Contrary to Foxe's observation, fenestrations were found in 5 of these 15 cases which involved all the cusps including the supernumerary one. In none of the 15 cases was there any associated congenital cardiac anomaly nor dilatation of the pulmonary artery.

Of the 30 cases, in 3 (10 per cent) there were bicuspid pulmonic cusps. One of the three patients concerned was a man who died of leukemia at the age of 23 years. At necropsy, the bicuspid pulmonic valve and dilatation of the pulmonary artery were discovered.

The second case of the three was that of a girl who died at the age of two months of cardiac insufficiency caused by stenosis of the pulmonary artery. There were no fenestrations in these cusps and no evidence of acute or chronic endocarditis. In the third case of the three, that of a boy 18 days of age, situs inversus with complete transposition was found at necropsy.

There were nine instances (33 per cent) of bicuspid aortic valve. Again in this group there were no clinical manifestations of valvular defect. Among these nine cases, however, there were five of coarctation of the aorta. The deformity seen at necropsy consisted of two valve leaflets, free at the margin in all cases but one, in that case vegetative endocarditis was present. These two valve leaflets were of approximately equal size and showed no evidence of previous inflammatory change which might confuse one in classifying the defect as acquired in nature. The case in which there was evidence of engrafted vegetative endocarditis had no features that would lead one to suspect previous inflammation. In two of these nine cases the coronary arteries came from behind one cusp and had separate openings. There were no fenestrations in these cusps. Two of the nine patients died of heart disease, one from hypertensive cardiac disease and one from vegetative endocarditis.

In three cases (10 per cent), the aortic valve had four cusps. These likewise were clinically silent defects. In all three specimens there was a

cuspid only 0.5 cm wide between the posterior and the right coronary cusp, this small cusp was well defined and was without evidence of previous inflammation. The margins of these cusps were remarkably free from change. There was one cardiac death and that was owing to coronary sclerosis. There were fenestrations in all the accessory cusps. In one case the remaining leaflets were involved while in the other two only the supernumerary cusp was fenestrated. Cardiac hypertrophy or dilatation of the aorta was not found.

SUMMARY

Thirty examples of variation in the number of semilunar cusps are reported. In all cases, the lesions caused no clinical signs or symptoms. This statement, however, would be misleading if mention were not made that seven of these cases were associated with other cardiac anomalies of clinical significance and one of them, a bicuspid aortic valve, was the seat of fatal vegetative endocarditis. The four-cusp pulmonary valve was most frequently found and was associated relatively seldom with other anomalies. There was an equal number of bicuspid pulmonary valves and four-cusp aortic valves. Bicuspid pulmonary and aortic valves seem the most important because they are associated with grave cardiac anomalies. There was no case in which a defect was present in both valves.

REFERENCES

- 1 ABBOTT, M. E. Congenital heart disease. In Nelson New Loose-Leaf Medicine, New York, Thomas Nelson and Sons, Part 2, Chapter 1, vol. 4, 1932, pp. 207-321.
- 2 BISHOP, L. F., JR., and TRUBEK, M. Bicuspid aortic valve, a differential study between inflammatory and congenital origin, Jr. Tech. Methods, 1936, xv, 111-131.
- 3 OSLER, W. The bicuspid condition of the aortic valves, Trans. Assoc. Am. Phys., 1886, 1, 185-192.
- 4 SIMONDS, J. P. Congenital malformations of the aortic and pulmonary valves, Am. Jr. Med. Sci., 1923, clxvi, 584-595.

SOME OF THE RECENT BIOCHEMICAL CONCEPTS OF GASTRIC SECRETION AND THEIR APPLICATION TO CLINICAL MEDICINE¹

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THIS paper is presented to summarize the data on gastric secretion which have originated from this department and which have been reported in a series of articles extending over several years. The investigation was undertaken with the idea of attempting to clarify some of the moot points in connection with the changes in the acid-base pattern of human gastric secretion, to learn, if possible, the secretory concentration of hydrochloric acid and of the neutral chlorides, to determine, if possible, the type of cell or cells secreting these neutral chlorides, and to study the inorganic phosphates during various phases of secretion. We were also interested in throwing more light on the nature of the substances which composed the protein and nonprotein nitrogen portion of gastric juice. These findings are given below and from them we have been able to propose a more satisfactory basis and method for titrating gastric secretion. We have also attempted to interpret the significance of these data in their clinical sense.

In order to better appreciate gastric secretion let us look upon the stomach as a membrane, a few millimeters in thickness, which forms the lining of the lumen in which the electrolytes and organic compounds of the blood are secreted or through which they are transferred. This membrane is composed of five main types of cell: (1) Chief body cells which secrete pepsinogen; (2) Parietal cells which secrete hydrochloric acid and perhaps neutral chlorides; (3) Mucus-neck cells which secrete mucus and salts; (4) and (5) The cylindrical epithelium of the foveola and enterochromaffine cells whose function in the formation of gastric juice is but poorly understood. Gastric juice is composed of the products of these cells and of the materials transferred from the blood and lymph to the surface of the stomach membrane. The secretory source from which come the proteins, nonprotein-nitrogen constituents and phosphates is not understood.

Our observations were made on the gastric juice of a group of 102 patients. The juice was aspirated before and at three consecutive half-hour periods after histamine stimulation¹. The majority of these analyses were made on gastric juice which was not only free from swallowed saliva but also from bile, many of the specimens, being quite clear and limpid, were almost totally free of mucus. Mucus was removed by filtration through fine filter paper.

¹ Read at St. Louis meeting of the American College of Physicians, April 23, 1937.

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OBSERVATIONS ON PATIENTS SECRETING HYDROCHLORIC ACID IN GASTRIC JUICE

The characteristic result of histamine stimulation on the secretion of gastric juice was a sudden increase in its volume. As the volume increased, the appearance of the fluid became clear and limpid. An elevation of the chloride and free hydrochloric acid concentrations accompanied this increased volume of secretion. There was always a concomitant decrease in the concentration of fixed base. This finding is illustrated in figure 1.

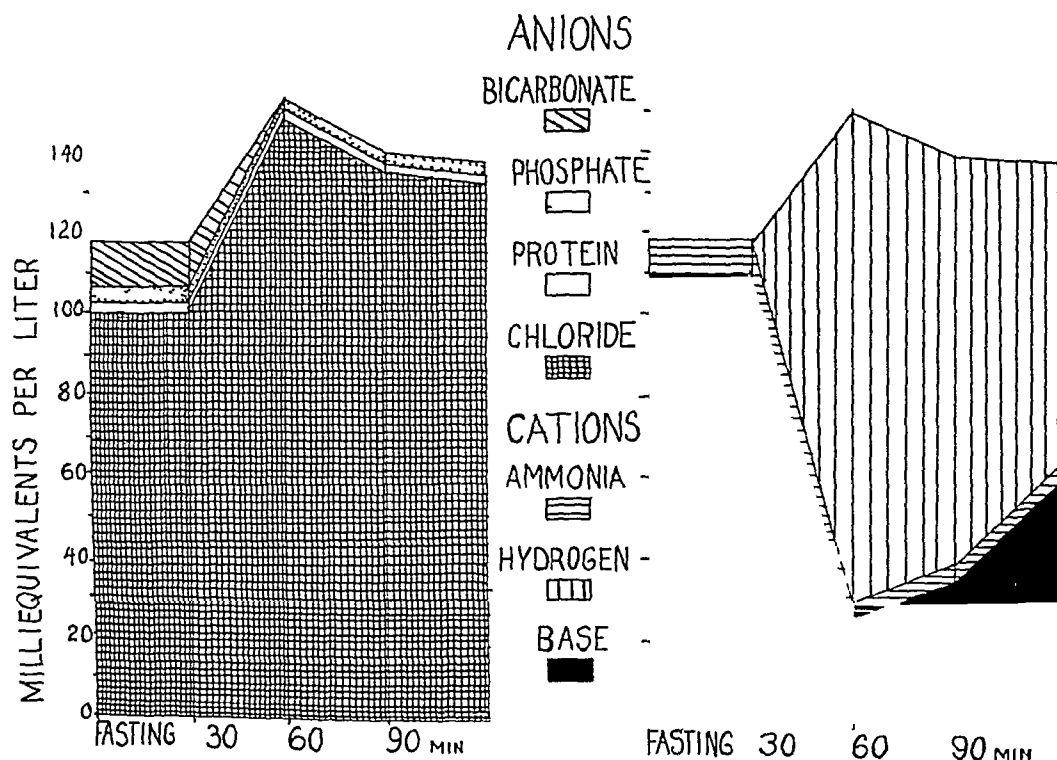


FIG 1 Illustrating the changes in the acid-base pattern of gastric juice during successive phases of secretion before and after histamine stimulation

When the total content of these substances was calculated from the concentration and the volume of secretion, it was shown that throughout the half-hour periods of observation the actual amounts of base secreted varied directly with the volume of secretion. The important factor in the increased volume of secretion was an increased production of hydrochloric acid. Consequently, during secretion of gastric juice the lowering of fixed base concentration represents dilution and not a decrease in the total volume secreted. As the stimulation of histamine waned there was a lowering in the concentration of total chloride and a more significant decrease in the hydrochloric acid content, to balance the latter change there was a corresponding increase in the concentration of fixed base. These findings were subsequently corroborated by Helmer²

Our investigations have shown that the chloride concentration in the extracted filtered gastric juice in which hydrochloric acid is found varied from 80 to 160 milliequivalents, the latter figure approximating the total electrolytic strength of the blood serum. In the juice from the Pavlov pouches of dogs, the limits are reported to be higher, 130 to 165 milliequivalents.

Phosphates have been noted in the gastric secretion of animals and humans by various investigators, and our determinations showed that they were also present in the gastric juice of our patients. The amounts present varied from 2 to 8 milliequivalents in those who were able to secrete hydrochloric acid. During the height of the secretion of hydrochloric acid the concentration of phosphate diminished markedly and correspondingly with the base. The total amount secreted in half-hour periods remained about the same.

The diminution in the concentration of hydrochloric acid during the end stages of secretion has been noted by numerous writers. Some have followed Boldyreff³ in believing this to be due to duodenal regurgitation; others,⁴ who have found the same phenomenon to occur in the gastric juices obtained after stimulation from Pavlov pouches in the stomach of dogs, do not believe this theory. In our own studies we found the decrease in hydrochloric acid to occur even when the juice showed no change from its clear limpid appearance and no trypsin. We believe that, although the concentration of hydrochloric acid may be reduced by duodenal regurgitation, this is a secondary reaction, and that the primary cause is a decreased secretion in volume of acid with an increased secretion of neutral chlorides.

It is customary to speak of neutralization of hydrochloric acid by gastric mucus. In the unfiltered specimen this may serve to dilute the acidity but that it does not exert any important neutralizing effect may be seen in the following table which is typical of the findings noted in several patients.

Case 54

Time Minutes	Description	pH	Volume c c	Milliequivalents per Liter		
				Free HCl	Total Chlorides as Cl	Base
Fasting	Mucus	1.7	1	78	125	47
30	Mucus +++	1.5	2	98	140	44
60	Mucus ++	1.4	2	121	158	40
90	Mucus	1.5	4	89	125	35

OBSERVATIONS ON PATIENTS NOT SECRETING HYDROCHLORIC ACID IN THE GASTRIC JUICE

There were many patients in whom achlorhydria was noted but in whom no organic basis for this condition was demonstrated. We classified these

cases as benign achlorhydria. In these cases it was questionable whether histamine caused any significant change in the volume of secretion. The chlorides fluctuated from specimen to specimen and in individuals. The lowest amount determined was 67 and the highest 118 milliequivalents per liter. The average was about 90 to 100 milliequivalents, i.e., approximately the same as for the chloride concentration in serum. In these patients the determination of bicarbonates was also important in that the amounts were significant, concentrations varying from 5.8 to 30.0 milliequivalents per liter were typical. The chloride and bicarbonate ions were balanced by fixed base and by ammonia, the former being the important ions and generally varying directly with the chloride, although somewhat higher, especially when the bicarbonates were elevated. The concentration of ammonia in these cases reached higher figures than in the acid-secreting patients and became a quantitatively important cation. The inorganic phosphates in the patients with achlorhydria varied from 2 to 16 milliequivalents. Half the determinations were above 8 milliequivalents per liter.

DISCUSSION OF ACID-BASE VALUES

It is enlightening to consider the acid-base balance in the patients with benign achlorhydria before entering into a discussion of its behavior in the juices containing hydrochloric acid.

The juice we obtained from the achlorhydria patients was mucoid in character. After filtration it became clear and, as noted above, always contained chlorides and bicarbonates. After histamine stimulation there was usually some change in the acid-base pattern but not of a degree to produce any new departure. It seems likely that the chlorides found in cases of achlorhydria originate in the fluid accompanying the mucus secretion. This point is emphasized here, since it is possible that the parietal cells secrete chlorides as both acid and neutral salts and that the amount of each secreted depends upon the nature of the stimulus, consequently, these cells have to be looked upon as a possible source of secretion of neutral chlorides in achlorhydria.

A real difference was observed in the gastric secretion of these patients whose resting juice did not contain hydrochloric acid but who secreted it after histamine stimulation. The latter specimens showed a marked increase in the chloride concentration which was always associated with hydrochloric acid. If the chlorides found in the achlorhydric fasting juice represent in part neutral chlorides secreted by the parietal cells, it would be expected that there would be a decrease in the total amount of neutral chlorides secreted after histamine stimulation had caused an outpouring of hydrochloric acid. We have noted a decrease in concentration of neutral chlorides, but our calculations do not show a decrease in the total amount of chlorides secreted during the half-hour periods. Therefore, it is probable that the excess secretion of chlorides was caused solely by the stimulated secretion of hydrochloric acid.

From our graph (figure 2) it is evident that the total chlorides may be secreted in a concentration equal to the total electrolytic concentration of the blood serum, approximately 160 milliequivalents per liter. However, there are many more instances in which the total chloride concentration of the extracted specimens is hypotonic. This may be due to two causes (a) The parietal cells may secrete chlorides at a concentration equal to or below the total electrolytic strength of the serum, or, (b) an isotonic parietal secretion of chlorides may be diluted by the lower chloride concentration of the fluid which accompanies the gastric mucus.

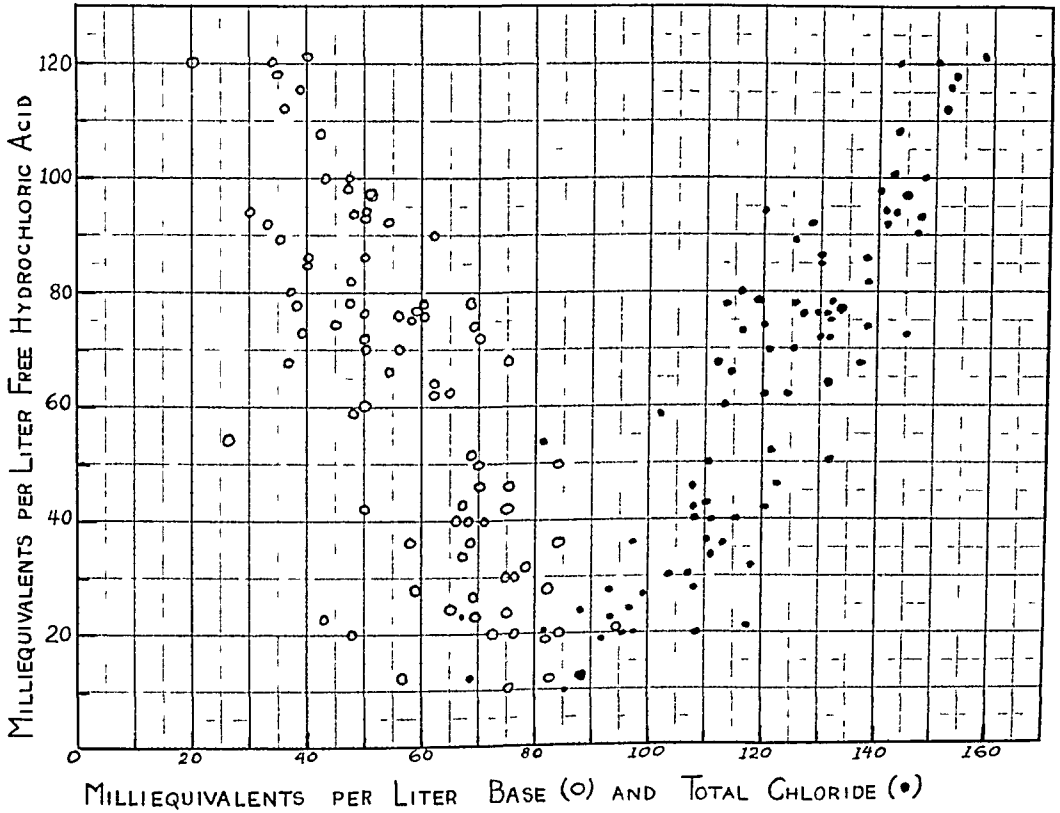


FIG 2 Illustrating the amounts of fixed bases and of the total chlorides of gastric juice as a function of the hydrochloric acid secretion

Although the chlorides of the extracted specimens were at times isotonic with the total electrolytes of the serum, hydrochloric acid was never so high, it did, however, approach this value. This may also be due to two causes (a) The parietal cell may secrete chlorides as both hydrochloric acid and neutral chlorides. In analyzing the data obtained on our specimens this condition has to be taken into serious consideration, (b) an isotonic parietal secretion of hydrochloric acid may be diluted by the hypotonic chloride fluid which accompanies the gastric mucus.

Many of the gastric aspirations were clear and limpid and contained only minimal amounts of mucus. The combined neutral chloride and

acid chloride concentration of several of this type of secretion were hypotonic. Whether there was sufficient neutral salt in the fluid accompanying the mucus to dilute a postulated isotonic hydrochloric acid secretion we cannot say.

At this point it is enlightening to consider Hollander's investigations.⁵ He obtained gastric secretion after histamine or food stimulation from Pavlov pouches made on the stomachs of dogs. From his findings he concluded that "The parietal secretion is essentially an isotonic solution of hydrochloric acid, and contains no fixed base. The alkaline component is an isotonic solution the principal constituents of which are neutral chlorides and bicarbonates, the concentration of the former being appreciably greater than that of the latter. Thus there can be no doubt that the chlorine content of the gastric juice of the highest degree of purity conceivable i.e. parietal secretion, is certainly in the form of the hydrochloric acid and not at all as alkaline or alkaline earth chlorides."

There can be little doubt from his words that he believes that the parietal cells secrete essentially only hydrochloric acid and at an isotonic concentration. He infers that the reason it is found in lower concentrations in the gastric juice is because it has been diluted by isotonic neutral salts or because it is neutralized, although only to a slight degree, by an isotonic solution of bicarbonates and that these latter substances are secreted by cells other than the parietal. If this conclusion is correct, it follows that at the onset of a free flow of "pure gastric juice" cells other than the parietal discontinue the secretion of chloride and bicarbonates. That this occurs in normal human gastric juice has not been proved.

At the risk of irksome reiteration it may be restated that, in the human gastric secretion, even the clearest specimens obtained were found to contain significant amounts of neutral chlorides. These it is true might represent that secreted with the mucus and it is very tempting to so credit their origin. If this were so, it would be reasonable to believe that hydrochloric acid was secreted into the human stomach in concentrations isotonic with the total blood electrolytes, as Hollander states is true in dogs. However, there is one reservation to the complete acceptance of this idea: hydrochloric acid is secreted into the stomach to provide a fluid of suitable hydrogen-ion concentration to permit pepsin activity. If "pure gastric juice" contained only hydrochloric acid, it would be of no value to the animal economy. Hollander says that the amount of organic material contained in his purest specimens was approximately zero.

We have found a fall in the protein nitrogen during the height of secretion, but significant amounts always persisted. We also made studies on the peptic activity of the specimens and found a direct relationship between the concentration of hydrochloric acid and the peptic activity. Perhaps in specimens of highest hydrochloric acid concentration more purified pepsin is to be found. The point to be made is that although hydrochloric acid of isotonic strength may possibly be secreted into the gastric juice the resultant

should not be called "pure gastric juice" A gastric juice without neutral chlorides may be a physiological and desirable one but so far it has not been demonstrated in man A gastric secretion lacking in pepsin is neither physiological nor desirable

PROTEIN AND NONPROTEIN NITROGEN CONSTITUENTS

In addition to the studies described above observations were also made on other constituents, to be found in human gastric juice which was essentially uncontaminated with regurgitated duodenal contents and saliva It was noted that, at pH 3.5, protein could be quantitatively precipitated by tungstates After acidification of the mucus-free, limpid, filtered gastric juice with glacial acetic acid, a portion of the protein-like material could be precipitated by making the solution 33 per cent with acetone This protein is crystallizable and has its isoelectric point at pH 3.5 We have called it gastro-globulin⁶ The amorphous material carried down with it all the pepsin and urease⁷ in the original solution Analyses of the crystals to determine their pepsin strength have not yet been made Urease had been sought for as a means of explaining the relatively large amount of ammonia and the small amount of urea which were found in the original gastric juice

It is important to note that the 33 per cent acetone filtrate contains a protein-like material to which is attached a carbohydrate molecule which forms osozones and which accounts for all the carbohydrates in the mucus-free gastric juice That it represents the carbohydrate of dissolved mucus is unlikely, since the 33 per cent acetone-soluble material is dialysable and does not react chemically as mucus

When the proteins and protein-like materials were removed from the gastric juice by tungstate at pH 3.5 the filtrates of a large series of cases were analysed for several nonprotein nitrogen constituents, namely non protein nitrogen, urea, ammonia, uric acid and amino acid It was found that in a series of patients secreting gastric juice of normal hydrochloric acid concentration the quantity of each was usually found within fairly restricted limits Average amounts were nonprotein nitrogen 25 to 35 mg per cent, uric acid 2 to 5 mg per cent, ammonia 5 to 7 mg per cent, urea 2 to 4 mg per cent, amino acids 5 to 7 mg per cent In benign achlorhydrias these constituents were present in about two-fold concentration, in pernicious anemia, in three-fold, in gastric carcinoma with achlorhydria, in four-fold This last finding might be of diagnostic significance in the differential diagnosis of certain cases of gastric ulcer and carcinoma⁸ Specimens of the gastric juice of patients with nephritis and blood-nitrogen retention were found to have even higher amounts of the various nonprotein nitrogen constituents

The foregoing data are of importance in understanding the significance of the conventional method of titration of gastric juice with NaOH when

Topfer's solution and phenolphthalein are used as indicators. At the end point of Topfer's, about pH 3.8, the free hydrochloric acid of the gastric juice is neutralized. However, at this point more than hydrochloric acid has been neutralized, for the iso-electric point of gastro-globulin is pH 3.5 and the other protein-like material is also precipitated at that point by tungstic acid. Consequently, it is fair to assume that in titrating the gastric juice to an end point with Topfer's solution as an indicator, one not only determines the free hydrochloric acid but also the combined acidity. Therefore, titration from pH 3.8 to an end point with phenolphthalein, pH 8.5, determines the buffer value of the gastric juice to this point. This may be of significance, but as yet we have not found out its true meaning nor determined the value of such an observation in clinical pathology. If such titrations are still done they should be given their real terminology, namely, buffer value of gastric juice from pH 3.8 to 8.5, and the usage of the term "combined acidity" should be discarded.⁹

DISCUSSION

The application of these more recent studies to routine clinical gastric analysis serves at least one useful purpose. It should limit the number of gastric analyses to those cases in which some definite information is desired. The information which we can gain from gastric analysis in general may be summarized as follows:

- 1 Presence or absence of hydrochloric acid
- 2 Normal or excessive secretion of mucus
- 3 Presence or absence of gross blood—not due to trauma
- 4 Elevated non-protein nitrogen in certain cases
- 5 Presence or absence of pepsin

These five potentialities may be further discussed with some advantage.

1 Titratable acidity of the gastric juice varies markedly in the normal individual and also depends upon the method used for stimulating its flow. It may be considered as within normal limits if it is above 20 milliequivalents or units.

In peptic ulcer it is usually high and in carcinoma it is usually low. If one of these pathologic conditions is suspected, a high or low titratable acidity (including achlorhydria) is of significance. However, an achlorhydria is not always an indication of organic pathological change, Keefer and Bloomfield¹⁰ have found that its incidence increases with age. A high titratable acidity is common in normal individuals.

In cases of macrocytic anemia, the proof of an achlorhydria is of fundamental import, but it must be remembered that the lowering of titratable acidity is to a large degree in direct relation to the decrease in the numbers of red blood cells and is, therefore, to be expected in association with the microcytic anemias.

2 In these days with so much attention being paid to the diagnosis of gastritis, an entity as yet not clearly understood, the demonstration of an increased secretion of gastric mucus may be of diagnostic importance

3 Free blood in the gastric contents affords direct evidence of some pathological change and necessitates further and more detailed study of the wall of esophagus, stomach and duodenum

4 An increase in the nonprotein nitrogen of the gastric secretion has been noted in several conditions. It is elevated in achlorhydria. It is especially high in the achlorhydria of cancer and may serve as a diagnostic aid in differentiating some cases of gastric cancer from peptic ulcer. It is noteworthy that it is markedly elevated in cases of nephritis in which there is blood-nitrogen retention. In these instances the stomach may be functioning as an organ of nitrogen excretion.

5 Pepsin has generally been reported as absent in cases of pernicious anemia, nor is it found in large infiltrating tumors of the stomach wall.

CONCLUSIONS AND SUMMARY

When gastric secretion stimulated by histamine begins, a fluid of changing acid-base equilibrium is secreted into the normal stomach. The element common to these changes is chlorine which is always found in the gastric juice. Appropriate stimulation will cause it to be secreted into the stomach in greater concentration than in the resting juice, and any significant increase in the chlorides is accompanied by an increase in the titratable acidity. It will often be accompanied by an increased volume of secretion of hydrochloric acid whose concentration in the extracted juice varies inversely with that of the fixed base (neutral salts). In human gastric secretion the absence of neutral salts has not been noted. Chloride concentration of the gastric juice equal to the total electrolytic strength of the serum has been found. In the majority of instances the former was below this level. The question of the monocellular source of the chloride secretion remains an open one.

The human gastric juice also contains a protein, gastro-globulin, which has been crystallized and is closely associated with pepsin and urease. There are one or more protein-like materials present and one or more of these have carbohydrate molecules attached. In this juice there are also such materials as ammonia, urea, uric acid and amino acid whose concentrations in the normal and certain abnormal individuals usually fall within predictable limits.

For reasons given above the usage of the term, *combined acidity*, is considered as incorrect and for clinical purposes the titration of gastric juice should be carried out to an end point with Topfer's solution, approximately pH 3.8, since at this point practically all of the acid chlorides both as hydrochloric acid and protein chlorides have been determined.

It is believed that gastric analysis should not be resorted to as a routine diagnostic procedure but that it should be performed only in those cases in which information concerning this secretion is of real importance

BIBLIOGRAPHY

- 1 MARTIN, L, MORGANSTERN, M, and CARROLL, M L Gastric secretion—the electrolytes before and their changes at various periods after histamine stimulation, *ANN INT MED*, 1932, vi, 91–128
Idem Acid-base balance of gastric juice, blood and urine before and at intervals after stimulation of the gastric juice by histamine, *Bull Johns Hopkins Hosp*, 1934, lv, 57–80
- 2 HELMER, O M Relation of secretion of mucus to acidity of gastric juice, *Am Jr Physiol*, 1934, cv, 28–36
- 3 BOLDYREFF, W The self-regulation of the acidity of the gastric contents and the real acidity of the gastric juice, *Quart Jr Exper Physiol*, 1915, viii, 1
- 4 MACLEAN, H, and GRIFFITHS, W J The factors influencing the concentrations of hydrochloric acid during gastric digestion, *Jr Physiol*, 1928, lxxv, 63
- 5 HOLLANDER, F Studies in gastric secretion IV Variations in the chlorine content of gastric juice and their significance, *Jr Biol Chem*, 1932, xcvi, 585
- 6 MARTIN, L Gastric juice I Studies on the proteins of the gastric juice of humans, *Jr Biol Chem*, 1933, cii, 113–130
- 7 *Idem* Gastric juice II Studies on the urea-splitting enzyme and pepsin in relation to the proteins, *Ibid*, 1933, cii, 131–136
Idem Studies on an urea-splitting enzyme found in gastric juice, *Bull Johns Hopkins Hosp*, 1933, lii, 166–172
- 8 *Idem* Total nitrogen and non-protein nitrogen partition of gastric juice obtained after histamine stimulation, *Ibid*, 1931, xlix, 286
Idem Protein nitrogen and non-protein nitrogen partition of gastric juice A clinical evaluation, *Jr Am Med Assoc*, 1933, c, 1475
- 9 *Idem* Recent investigations permitting a new interpretation of the results of the conventional titration of gastric juice, *Am Jr Digest Dis and Nutr*, 1934, i, 330
- 10 KEEFER, C S, and BLOOMFIELD, A The significance of gastric secretion, *Bull Johns Hopkins Hosp*, 1926, xxxix, 304

SACCULAR ANEURYSM OF THE T A CLINICAL STUDY OF 63

By R H KAMPMEIER, M D , F A C P , I

"There is no disease more conducive to clinical h
aorta"—Osler

ANEURYSMS of various types have long be
type to be described came to be known as *false an*
rupture or wounding of an artery, the sac which
the adjacent tissues or newly formed connectiv
aneurysm is the term applied to a communicatio
vein If it is direct, the lesion is known as *ane*
there is an interposed sac it is named *varicose an*
rarely be due to traction or erosion resulting from
occasionally may be of mycotic, or of embolic ori

True aneurysms are those in which one or mo
the wall of the tumor The least common of th
aneurysm in which rupture of the intimal coat all
between the intima and media for varying distan
tion of a new tube The most frequent aortic :
aneurysm in which usually only a portion of the
form or cylindrical form, though occasionally
branches may be dilated, and it is then known as a
there is the *saccular aneurysm*, a circumscribed bu
sel with the formation of a sac connected to the l
by a definite ring It is the last disease entity
concerned

HISTORICAL

At the request of the Council of the Sydenham
translated and edited selections from the principal write
from the earliest times to the end of the eighteenth ce
under the title of "Observations on Aneurysms," in 18
literature up to the nineteenth century, appearing below
this work or from Major's² "Classic Descriptions of

Galen,¹ in the second century, first described fal
trauma to an artery Four centuries later, Aetius,¹ in
cluded lesions due to rupture of an artery without exte
in the neck, saying, " it very commonly happens

cially in the chest, or about the spleen and mesentery, where violent throbbing is frequently observable"

Late in the sixteenth century, Ambroise Paré² wrote the first published note of the relationship of aneurysm to syphilis. He said "The Aneurismes which happen in the internal parts are incurable. Such as frequently happen to those who have often had the unction and sweat for the cure of French disease, because the blood being so attenuated and heated therewith that it cannot be contained in the receptacles of the Artery, it distends it to that largeness as to hold a man's Fist, Which I have observed in the dead body of a certain Taylor who by an *Aneurisma* of the Arterious vein suddenly whilst he was playing at Tennis fell dead, the vessel having broken, his body being opened I found a great quantity of blood powred forth into the capacity of the Chest, but the body of the Artery was dilated to that largeness I formerly mentioned, and the inner coat thereof was bony"

Richard Wiseman,² in his works published in 1696, gave two causes for internal aneurysms. "1 The internal Cause is, the impetuosity of the Blood, which moving with greater violence in its Channells than the Artery can sustain, doth force its way through the side of the Vessel. Secondly, from the quality of the Blood, which being too sharp or thin, erodes the Vessel, or, being highly fermented by other causes, bursts through all"

Lancisi,¹ 1728, published an extensive discussion of aneurysm. He applied the terms "true" and "false" but not in the modern sense. True aneurysms were those in which a weak arterial wall occurred either from external trauma or from internal causes as "deficiency or debility of the villi". False aneurysms were those due to "increased power of the impulse, produced by violent efforts in porters and trumpeters". In his Proposition XXXII "On the mode of formation, the causes, and symptoms of a syphilitic aneurysm" Lancisi described skeletal erosion by an aneurysmal sac. "As an acrid fluid, distilling from the aneurysmal cyst or sac, may penetrate as far as the bones or ligaments, which it may gradually corrode, and wear away, so, on the contrary, it may sometimes happen that the lymph, abounding in syphilitic humours, may, first of all, give rise to congestion in the bones and ligaments, but by and by, having become more acrid, and settling in the external coat of the artery, it may begin to corrode, and thus to dilate it into an aneurysm". He also discussed mercury as a cause of aneurysm. "The whole influence of mercury in giving rise to aneurysms consists in the strength of the impulse by which the weakened lymph and blood are forced and tossed about on all sides". Further, he believed that "mercurial fluid" in the vessels caused distention of them just as it caused swelling of the salivary glands. Lancisi also described the clot which often forms in aneurysmal sacs, as follows, "The polypous body, by obstructing entirely the canal of the vessel prevents the direct passage of the blood, interrupting the circulation, and compelling the fluid to take a collateral route. Hence from this cause, the pulse is often obliterated at the wrist, as happened to the Marchioness Paulutio"

In 1736, Petit¹ described aneurysms due to puncture of a vessel as *aneurysms of effusion*, and others as *aneurysms by dilatation*. He pointed out that the latter presented a thrill, rarely present in the former, and that by applying the ear, a distinctive sound could be heard.

William Hunter,¹ in 1757, published a detailed account of the case of a patient with an aneurysmal sac pointing through the chest wall, which oozed blood for some weeks before death. An autopsy was done. In his discussion he used the terms "true" and "false" in the modern sense. Also he described the symptoms of pressure he had encountered in five cases of aneurysm.

Donald Monro,¹ 1760, in a long paper on the subject of aneurysm, made the first reference, in the English literature, to syphilis. He said, "Sometimes a scorbutic or venereal taint, or some other acrimony in the blood, has been accused"

In 1761, Morgagni² published "The Seats and Causes of Disease" In 1725 he had had the opportunity to perform an autopsy on the body of a young woman who had died during sexual intercourse A small aneurysm was found, one-half inch above the aortic valves, which had ruptured into the pericardium The first description of the gross pathology of syphilitic aortic disease is as follows "That is to say, in some places whitish marks of a future ossification occurred, in others, some small foramina, as it were, had begun to be formed, and in still other places were paralleled furrows, drawn longitudinally, and in this manner was the surface of the artery unequal here and there" Even earlier, in 1708, Morgagni had noted similar changes in the aorta of another young woman who had died due to aneurysmal rupture

Corvisart³ described, in 1806, various symptoms and signs which may be encountered in aortic aneurysm, pointing out that the diagnosis is difficult unless the sac points externally He called attention to the thrill, retro-manubrial dullness on percussion, smallness and inequality of the pulse, and a whistling sound when the sac compresses the trachea Bertin⁴ in 1833, and Flint⁵ in 1859 added further to the clinical description of aneurysms of the thoracic aorta In 1878, Oliver⁶ published a short note describing tracheal tug

Welch,⁷ in 1875, presented data attempting to prove that syphilis was the cause of aortic aneurysm in 66 per cent of 53 cases of aneurysm found at autopsy in soldiers He described his gross findings, and stated, "this disease of the aortic coats may retrogress but if extensive or severe, as a rule it is followed by one of three fatal phases—formation of aneurysms, implication of aortic valve, or hypertrophy with or without dilatation of one or more of the heart's cavities" The paper was very unfavorably received and its discussants, among whom was Sir William Gull, openly expressed their unbelief An unfriendly review soon followed in the *Lancet* Welch answered this by a published letter in the same journal

In 1888, Thoma⁸ wrote concerning the pathology of aneurysmal formation, and considered as its cause, arteriosclerosis due to marasmus, lead, syphilis, gout, et cetera

It had been recognized for some time that syphilis was mainly a vascular disease, when Dohle⁹ in 1895 discussed the microscopic changes in syphilitic aortitis and their bearing upon the formation of aneurysm In this paper he reviewed a case which he had reported in 1885, describing the pathology of syphilitic aortitis

Then came the discovery of the *Spirocheta pallida* by Schaudinn and Hoffmann¹⁰ in 1905, in the primary lesions of syphilis In the following year, Reuter¹¹ described the organism in the wall of the aorta in aortitis

The importance of syphilis as a cause of aneurysm thus became established

MATERIAL

Studies of large series of cases collected from the literature have appeared in the past, but such material drawn from many sources suffers from lack of uniformity in study Hare and Holder¹² and Boyd¹³ have published the largest collected reports

From 1905 to 1935 inclusive, 1038 patients were admitted to the wards of Charity Hospital, in New Orleans, in whom a diagnosis of aneurysm of the thoracic aorta was made At the Vanderbilt University Hospital, from 1925 to 1936 inclusive, 75 patients were so diagnosed in the wards and clinics The combined material from the two institutions (1113 patients) represents a recorded experience with this disease of such magnitude as to justify analysis, since it constitutes the largest material subjected to review

From the 1113 hospital records of aneurysm of the thoracic aorta, there have been selected 633 for this study. The remainder were excluded because they did not meet the rigid criteria demanded for inclusion. These criteria were as follows:

- 1 The demonstration of aneurysm at necropsy (165 cases)
- 2 A history and physical findings compatible with the presence of aneurysm, and in addition either, (a) a visible expansile tumor eroding the chest wall (120 cases) or, (b) the roentgenologic evidence of a saccular aneurysm arising from the aorta

On the basis of such rigid selection, it seems that any error is on the side of failure to include in the study some cases which were discarded.

INCIDENCE

The aorta is the most frequent vessel to be involved in the formation of aneurysm. Further, it is the thoracic portion which is especially affected. The frequency of aneurysm in the thoracic aorta as compared with other vessels is shown in table 1. (Aneurysms due to trauma are not included.) Seventy-three of the cases of aneurysm of the abdominal aorta were studied and reported by the author.¹⁴

TABLE I
Diagnosis of Aneurysm in the Charity Hospital Group
(1905 to 1935)

Site of Aneurysm	Number
Thoracic aorta	1038
Abdominal aorta	95
Carotid artery	12
Innominate artery	10
Subclavian artery	3
Iliac artery	2
Pulmonary artery	2
Anterior vertebral artery	1

The incidence of aortic aneurysm fluctuates within wide limits in various countries, and in the United States it varies with the section of the country, because of the unequal distribution of the negro race. Obviously the incidence will differ as between private and charitable institutions.

There are surprisingly few publications dealing with the incidence of aortic aneurysm in large series. Those available have been considered from two viewpoints, the clinical and the necropsy incidence.

The clinical incidence will vary a great deal with the accuracy of the study. Generally patients studied on hospital wards will show a greater number of aortic aneurysms than patients in the Out-Patient services. Boyd¹³ says aneurysm is 15 times more common in hospital series than in ambulant series, but gives no data as proof of this. In table 2 have been assembled the statistics of the clinical diagnoses of aortic aneurysm in

TABLE II
Frequency of the Clinical Diagnosis of Aortic Aneurysm in Various Hospitals

Author	Hospital and Years	Number of Aneurysms	Ratio per Patient
Browne ¹⁶	St Bartholomew's Hospital, 1867-83	228	1 350
Eichors ¹⁶	Zurich Medical Clinic, 1884-1901	28	1 1200
Wolpert ¹⁶	University of Berlin, O P D, 1895-1905	55	1 1359
Dahlen ¹⁶	Stockholm (Hospital), 1897-1906	22	1 790
Osler ¹⁷	Johns Hopkins Hospital (Medical Wards), 1889-1909	231	1 105
Allen ¹⁷	Melbourne Hospital	298	1 157
Lemann ¹⁸	Touro Infirmary, O P D	47	1 300
Kampmeier	Vanderbilt University Hospital, O P D and wards, 1925-1936	75	1 1080
Kampmeier	Charity Hospital, wards only, 1905-1935	1038	1 756

various hospitals throughout the world. They are not comparable because some are from ward studies and some from out-patient series. Further, the statistics probably include aneurysms of various types, whereas the present study deals only with the saccular variety. At Vanderbilt University Hospital the diagnosis was made 75 times giving an incidence of about 1 1080. However, if this is corrected by applying the criteria of the present study only 44 cases of the 75 are found acceptable, the incidence then becomes 1 1840. In the 30 year period covered by the Charity Hospital series, there were 774,774 admissions, and since the diagnosis of aortic aneurysm was made 1038 times, the incidence was 1 756. But if only the 593 acceptable cases are taken, the ratio is 1 1306 admissions.

In table 3 are given the results of various necropsy studies. Lucke and Rea ¹⁶ have collected the material from Germany, Austria, the Scandinavian

TABLE III
Incidence of Aortic Aneurysm at Necropsy in Various Countries and in Certain Hospitals in the United States

	Hospital	Necropsies	Ratio
India	Calcutta Medical College ¹⁷	5,900	1 196
Germany and Austria ¹⁶		160,145	1 111
Scandinavian countries ¹⁶		5,490	1 109
Great Britain ¹⁶		36,500	1 74
United States		16,200	1 41
Lucke and Rea ¹⁶	Philadelphia General Hospital, 1867-1916	12,000	1 43
Osler ¹⁹	University of Penn Hospital, 1875-1916	2,200	1 34
Warthin ²⁰	Johns Hopkins Hospital (Med Wards)		
	University of Michigan Hospital, 1909-1929	1,675	1 52
Kampmeier	Vanderbilt University Hospital, 1925-1936	1,653	1 331
Kampmeier	Charity Hospital, 1905-1935	12,053	1 73
Author's Negro male	Med Service, Charity Hospital (4 years)	284	1 18

countries, Great Britain, and from the United States. Unfortunately the statistics for this country are probably not representative, because of the total of 16,200 necropsies, 14,400 occurred in Philadelphia Hospitals and in Johns Hopkins Hospital which probably admitted more colored patients than comparable northern hospitals. Boyd¹³ states that postmortem statistics indicate that aneurysms account for 0.1 to 0.9 per cent of deaths in American cities. In the present study, it was found that at Vanderbilt University Hospital, where relatively few negroes are admitted, the incidence was one saccular aortic aneurysm to 410 necropsies. At Charity Hospital 12,053 necropsies had been performed in the 30 year period, with an incidence of one case of thoracic aneurysm to 73 necropsies. In order to contrast the incidence of postmortem proved aortic aneurysms in negro males alone with that of the general hospital frequency the following figures are of interest. In a four year period 284 necropsies were done on patients from the 29 bed, negro male division of the medical service under my care at Charity Hospital. Among these were 15 cases of saccular aortic aneurysm, giving an incidence of 1/18 necropsies.

TABLE IV

Incidence of Aortic Aneurysm in 5 year Periods as Related to Hospital Admissions

Years	Accepted Cases of Aneurysms	Hospital Admissions	Ratio of Aneurysms to Admissions
1906-1910 inclusive	42	47,736	1/1136
1911-1915 inclusive	79	74,117	1/925
1916-1920 inclusive	91	90,613	1/995
1921-1925 inclusive	109	105,330	1/966
1926-1930 inclusive	136	166,086	1/1221
1931-1935 inclusive	134	282,480	1/2854

Table 4 is of interest because it may indicate the trend of the occurrence of aneurysm. The incidence of aneurysms is analyzed with reference to admissions. In the single years as well as for the 30 year period, the cases accepted for this study were roughly about one-half of the cases diagnosed. Thus this table presents no special selection. This decrease, by more than half, in the frequency of aneurysm lends support to the belief that the lesion is becoming more infrequent, whether due to more frequent and adequate treatment, or to some other cause.

ETIOLOGY

Syphilis This disease is accepted as the specific etiologic factor in the great majority of cases of aneurysm of the larger vessels.

Though it is recognized that the history of a genital sore does not necessarily mean that the sore was syphilitic in nature, such presumptive evidence will, nevertheless, be presented. A history of a genital chancre was obtained

from 241 patients (38 per cent) and of a labial lesion in one instance. Only five of the 242 patients were women, and each of these five gave a history of a vulval lesion.

The date of the primary sore is no doubt inaccurate in many of the patients, especially among the negroes, but in table 5 are given the data as

TABLE V
Time Elapsed from Chancre to Onset of Symptoms

Years not specified	22
1-5 years	21
6-10 years	30
11-15 years	45
16-20 years	68 (one lip)
21-25 years	24
26-30 years or over	32
Total	242

recorded regarding elapsed time from the sore to the date of history taking. The intervals ranged from 5 to 30 years. Noteworthy is the fact that the second decade (11 to 20 years) before admission included 113, or about one-half, of the aneurysm patients reporting a genital lesion. It thus appears probable that aortic aneurysms make themselves evident from 10 to 20 years after infection in untreated individuals. Among the 4000 cases collected from the literature by Boyd,¹³ 200 gave a history of a primary lesion, and an average of 20 years had elapsed from the time of infection to the date of diagnosis of aneurysm.

The blood Wassermann test presents more acceptable evidence of syphilis than a history of a genital lesion. This test was done in 467 patients or 73.7 per cent of the material. (In the remainder the test was not done, either because the patients were seen in the first decade covered by this study, or because early death after entering the hospital prevented it.)

Of the 633 cases, 467 had a Wassermann test, 112 had neither a serological test nor a history of a genital lesion, and 54 had had a primary lesion but no Wassermann test. Of the 467 tested cases, 291, or 62 per cent, gave a positive Wassermann reaction, and 176, or 38 per cent were negative. Among the 291 positive reactors were 118 (40.5 per cent) with a history of a genital lesion. Among the negative reactors were 70 (39 per cent) who had had a sore.

As evidence of syphilis, then, there was a positive Wassermann test or a history of a genital sore (with or without a negative Wassermann reaction) in a total of 415 cases. In addition there were two cases without either of these criteria, but with a positive spinal fluid. Thus there was clinical evidence of syphilis in 417 cases, or in 65 per cent. Necropsy was done in 35 cases in which the Wassermann test was negative, and in 73 cases without serological study. In these 108 examinations the gross or microscopic diagnosis of syphilis was made 33 times (three of these had

had a chancre) It is thus found that 447, or 70 per cent, of the cases in this study may be accepted as being definitely syphilitic The necropsy protocols of the early years of the period covered, and of the coroner cases were brief and confined to gross findings, thus accounting for the few cases presenting pathological evidence of syphilis in the absence of clinical studies It seems quite obvious that if satisfactory examinations had been carried out in the early cases that had neither Wassermann tests nor careful postmortem studies, the proof of syphilis would have been much more frequent

To obtain more accurate information in this respect, the Vanderbilt cases, and the cases of the last decade of the Charity Hospital were separately analyzed Among the 44 Vanderbilt Cases were 16 with either a negative or no serological test Nine of the 16 had either a history of a sore, positive necropsy diagnosis, or aortic insufficiency as evidence of syphilis These in addition to those with positive Wassermann tests give an incidence of proved syphilis in 84 per cent Of the 269 cases of saccular aneurysm, occurring in the last 10 years of the Charity Hospital study, 117 had either a negative or no Wassermann test Of these 36 had a history of genital sore, 17 more had a necropsy diagnosis of syphilis, and 12 had aortic insufficiency These cases in addition to the 152 with a positive serological reaction give an incidence of syphilis in 81 per cent

Arteriosclerosis Arteriosclerosis is occasionally thought of as a cause of aneurysm That atheroma may be a secondary factor in conjunction with syphilis seems probable, but the location of the process in the mesaorta which results in a bulging of the aortic wall, with its predominant intimal involvement, indicates that arteriosclerosis is not a major etiologic factor Old age itself does not offer proof that arteriosclerosis is the cause of aneurysm In this series, there were 19 patients over 50 years of age, in whom necropsy showed syphilitic lesions Three of these were over 70 years old

Hypertension This condition has in the past been assigned a rôle in the production of aortic aneurysm As in the case of arteriosclerosis, if hypertension plays any part at all, it must be only secondary in nature, since it does not lead to mesaortitis Possibly hypertension in the presence of disease of the media may aggravate the tendency to saccular dilatation It is important to emphasize in this connection that only hypertension, which is unassociated with aortic insufficiency, might be of significance In table 6 are analyzed 64 cases of aneurysm with a systolic blood pressure of over 160 mm

No cases of aneurysmal sac on a mycotic or embolic basis were found, nor were there any due to tuberculosis

Race Aneurysm appeared most often in the negro This is not surprising because of the greater incidence of syphilis in this race and because treatment is so commonly neglected Of the 633 cases, 482, or 76 per cent,

TABLE VI

Sixty-Six Cases of Aneurysm with a Systolic Pressure of Over 160 mm

Age	Wass Pos		Wass Neg		No Wass		Syphilis Autopsy	Atheroma Autopsy	No Data Autopsy
	Cases	Aortic Insuf	Cases	Aortic Insuf	Cases	Aortic Insuf			
26-35 yrs	2	—	1	—	—	—	—	—	—
36-45 yrs	11	5	5	4	2	1	1	—	1
46-55 yrs	12	3	10	3	1	—	4	—	2
56-65 yrs	9	3	6	1	—	—	—	—	—
66-75 yrs	4	1	2	—	—	—	—	1	—

were negroes, and 24 per cent, or 151 were white (This series included one Filipino and one Puerto Rican)

In the Vanderbilt University Hospital group the incidence of white to colored patients with aneurysm was 1 53. In the Charity Hospital group it was 1 31, whereas the ratio of white to colored hospital admissions was 12 1 in the last decade. Osler's¹⁹ Johns Hopkins Hospital series showed a ratio of white to negro patients with aneurysm of 26 1, but with an admission ratio of 4 1. Lucke and Rea,¹⁰ in Philadelphia, found a ratio of white to colored patients of 23 1 while admissions were 15 1.

Sex Since syphilis is the accepted etiologic factor in production of aneurysms of the large vessels, and because syphilis is found more often in the male, aneurysm of the aorta would be expected to develop more often in this sex. This is shown to be true in the present series. Thus, 379 (59.8 per cent) were negro males, 131 (20.8 per cent) were white males, 103 (16.1 per cent) were negro females, and only 18 (2.8 per cent) were white females. To express it in another way, the incidence of thoracic aortic aneurysm was in the ratio of, male to female, as 37 1 in the colored, and as 79 1 in the white group. If these figures are averaged, the ratio is 58 1. Boyd¹³ in his 4000 collected cases found a ratio of 58 males to 1 female, and Lucke and Rea¹⁰ in necropsy statistics, found it to be 42 1.

Age Generally, the members of the medical profession think of aortic aneurysm as occurring in patients of about 40 to 50 years of age. Age in itself is a minor factor, however. Only the years elapsed since the primary syphilitic infection are of importance.

Therefore, in the case of the negro, whose sex-life often begins early, and whose syphilitic infection is more often acquired earlier, it is not uncommon to see full-blown cardiovascular syphilis at a comparatively early age. In this series, nine gave an age of from 20 to 25 years, seven negroes and one white were males, and one was a negress. In the 26 to 35 year old group, there were 62 males and 18 females of the colored race, and 8 males and 3 females of the white race. Sixteen per cent of all the cases were in persons of less than 35 years of age.

The highest incidence of aortic aneurysm in the negroes was in the 36 to 45 year old group, where there were 130 males, and 42 females, or 32.3 and 40.7 per cent of their respective groups. The greatest incidence among white males was in the 46 to 55 year group, with 46 cases, or 34.5 per cent. Among white females six cases, 33 per cent, appeared in each 10 year span of 46 to 55, and 56 to 65 years. Table 7 presents the distribution of aortic aneurysms with regard to age, sex, and race.

Occupation (Table 8) Hard manual labor has been accepted as being of great secondary importance to syphilis in the causation of aortic aneurysm.

TABLE VII

Distribution of 633 Aortic Aneurysms, as Regards Age, Sex and Race

Age in years	Other Races	Negro Males	White Males	Negro Females	White Females
20-25 yrs inclus	—	7	1	1	—
26-35 yrs inclus	—	62	8	18	3
36-45 yrs inclus	1	130	31	42	1
46-55 yrs inclus	—	115	46	29	6
56-65 yrs inclus	1	45	31	12	6
66-75 yrs inclus	—	18	13	1	1
76-85 yrs inclus	—	2	—	—	1
Age not given	—	—	1	—	—
Total	2	379	131	103	18

TABLE VIII

Occupation of 633 Patients with Aortic Aneurysm

	Negro	White
Males		
Laborer	280	49
Farmer	25	10
Skilled laborer	4	11
Clerk	1	9
Baker	—	4
Barber	1	1
Watchman	1	1
Cook or waiter	9	2
Peddler	2	1
Railroadman	—	6
Merchants	—	3
Chauffeur	3	—
Minister	2	—
Porter	8	—
Miscellaneous	6	4
No occupation given	37	30
	379	131
Females		
Housework	65	6
Housewife	5	10
Laundress	9	—
Cook	9	—
No occupation	15	2
	103	18

This led Osler to join 'Venus, Mars and Vulcan' as a triad responsible for aneurysm. The rôle of heavy work is borne out in the present study. The table indicates the large percentage of males who engaged in hard work as common labor or in farming.

As was pointed out above, the incidence of aneurysm in females is one to about six in males, whereas the incidence of syphilis in the two sexes is usually given as four females to six males. The difference in these ratios is probably due to less exposure and lighter work in the female, though it must be recognized that generally syphilis runs a more benign course in the female.

ANATOMICAL CLASSIFICATION

From an anatomical viewpoint, aneurysms may be classified according to the portion of the intra-thoracic aorta involved. This anatomical classification is of clinical value from the standpoint of the symptomatology, physical signs, prognosis, and complications which may be expected.

This paper will consider the clinical aspects of aneurysmal sacs arising from the four main portions of the thoracic aorta—ascending, transverse, and descending segments of the arch, and the descending thoracic aorta. In the study of the 633 cases, two additional classifications were added. In one group the site of the sac could not be accurately placed, and therefore these 14 cases were labelled merely as 'aneurysms of the arch'. The second group consisted of 23 cases in which there were two or more sacs which obviously might lead to mixed clinical pictures.

The detailed study of this paper is therefore based upon 596 cases distributed among the four anatomical divisions of the thoracic aorta. See table 9 for the distribution as related to sex and color.

TABLE IX
Anatomical Site of Sac as Related to Sex and Color

Aortic Segment	Negro Males	White Males	Negro Females	White Females	Other Races
Arch	6	6	1	1	—
Ascending arch	129	39	40	6	—
Transverse arch	124	34	40	5	2
Descending arch	85	40	18	4	—
Thoracic aorta	22	5	3	—	—
Multiple sacs	15	7	1	2	—

For years saccular aneurysm arising from the ascending arch has been known as "aneurysm of signs". Sacs arising from the aortic arch, between the aortic valve and origin of the innominate artery, may attain great size, often with few symptoms, and tend to point anteriorly through the chest wall. There were 214 examples of this type. For the sake of simplicity,

four cases in which the sac arose from the sinuses of Valsalva have been included in this group

Transverse arch aneurysm is known as "aneurysm of symptoms" Saccular aneurysm was found at this site in 205 cases This segment of the arch is intimately related to the esophagus, trachea, left bronchus and left recurrent laryngeal nerve Because of narrowness of the thoracic inlet and the presence of these vital structures, it is obvious that aneurysms of the transverse arch are prone to produce symptoms since, as they expand, they encroach upon these structures

The descending arch lies to the left of the third to sixth dorsal vertebrae, close to the esophagus and left bronchus Often a sac in this area is silent, but when it points, it does so posteriorly through the chest wall to the left of the spine There were 147 cases of aneurysm of this segment

Much less common than any of the above groups are aneurysm of the descending thoracic aorta, that part of the aorta extending from the sixth to twelfth dorsal vertebrae Sacs arising from this portion often reach immense size without symptoms or signs, and it is in this group that the clinician is most likely to be surprised upon roentgen-ray or postmortem examination There were 30 cases of aneurysm in this division of the aorta In his 4000 collected cases, Boyd¹⁸ found the ratio of sacs in these segments to be, in order, 10-7-3-1, in the present study the ratio is 7-7-5-1

CHIEF COMPLAINT

In table 10 are listed, with their frequency, the complaints which brought the patients to the hospital These will be more fully considered under a discussion of symptomatology

TABLE X
Chief Complaint

	Ascend Arch (214 cases)	Trans Arch (205 cases)	Descend Arch (147 cases)	Descend Thor (30 cases)
Pain	112	114	103	25
Dyspnea	94	80	42	3
Cough	35	45	34	3
Tumor	37	28	10	2
Palpitation	18	13	8	3
Hoarseness	10	19	20	—
Dysphagia	5	13	5	—
Hemoptysis	2	3	6	1
No history	9	7	8	1

Most important is the fact that pain was the main symptom the patients complained of This is significant if the figures are compared with those of the table of symptoms, where dyspnea is found more frequently than pain, though it appears less often as a complaint

SYMPTOMATOLOGY

The duration of symptoms in the majority of cases had been from two to 12 months. In table 11 the cases are grouped according to the duration

TABLE XI
Duration of Symptoms

	Ascend Arch (214 cases)	Trans Arch (205 cases)	Descend Arch (147 cases)	Descend Thor (30 cases)
1 wk or less	23	7	2	1
1 to 4 wks	26	31	18	5
1 to 3 mos	40	38	26	3
3 to 6 mos	36	41	28	8
6 to 9 mos	15	16	11	2
9 to 12 mos	32	23	18	4
12 to 18 mos	9	10	7	2
18 to 24 mos	14	12	10	1
2 to 3 yrs	8	7	7	3
4 yrs	2	1	—	—
5 yrs	2	5	—	—
6 yrs	4	—	3	—
10 to 15 yrs	1	2	—	—
Yrs ?	2	—	2	—

of symptoms, whenever this was recorded. The time elapsed from the onset was no more than one year in 71 per cent of the ascending, 76 per cent of the transverse, 70 per cent of the descending, and 76 per cent of the descending thoracic segment cases. In a few instances in each group, symptoms had been of less than a week's duration, and in an occasional instance as long as from 5 to 15 years.

In table 12 are given the symptoms, and frequency of these, in saccular aneurysms of the thoracic aorta.

TABLE XII
Symptoms of Aneurysm of the Thoracic Aorta

Symptoms	Ascend Arch (214 cases)	Trans Arch (205 cases)	Descend Arch (147 cases)	Descend Thor (30 cases)
Pain	132	123	106	26
Dyspnea	140	131	76	10
Cough	117	119	75	9
Palpitation	32	18	11	3
Hoarseness	34	63	36	2
Dysphagia	16	40	12	2
Hemoptysis	18	17	19	3
Tumor	37	32	10	2
Edema of legs	43	24	14	1
"Choking spells"	2	15	2	—
Vertigo	17	20	7	—
Sputum	42	45	26	5
No history	9	7	8	1

Pain was present in about 60 per cent of the cases of ascending and transverse arch groups. It occurred in 72 per cent of the descending arch and in 86 per cent of the descending thoracic aneurysms. Usually the pain was described as pressing, boring, and, more often than not, constant in nature. Undoubtedly in most instances such pain can be explained by pressure of the sac either upon certain structures, or, more often, on portions of the chest wall giving pain of segmental distribution. In some cases the pain was described as of anginal type, probably due to either involvement of the coronary orifices in the syphilitic aortitis, or to aortic insufficiency, either of which would lead to myocardial ischemia.

The site and radiation of pain is of importance because of the erroneous diagnoses which often result, and therefore these features have been tabulated in table 13. In a fair number the detailed site of pain was not given,

TABLE XIII
Site and Radiation of Pain in Aortic Aneurysm

Site of Pain	Ascend Arch (214 cases)	Trans Arch (205 cases)	Descend Arch (147 cases)	Descend Thor (30 cases)
Chest, in general	35	37	16	—
Chest, right	31	3	4	—
Chest, left	2	20	25	6
Chest, precordial	11	8	4	—
Chest, retrosternal	5	9	4	—
Chest, substernal	2	6	—	1
Neck	17	6	4	—
Face or head	2	2	4	—
Shoulder, right	13	7	2	—
Shoulder, left	1	10	10	1
Shoulder, both	3	5	2	—
Arm, right	15	5	—	—
Arm, left	4	10	8	1
Arm, both	1	4	3	1
Back, in general	—	—	2	—
Back, interscapular	9	13	6	8
Back, right	—	—	3	—
Back, left	—	—	25	4
Flank, left	—	—	—	2
Epigastrium	—	7	11	2
Abdomen	9	—	10	12

the patient's statement for "chest-pain" being all that was recorded. The site of the sac accounts for the frequency of pain in the right chest in the ascending arch group, and in the left chest in the transverse, descending and thoracic aorta group. (Transverse arch aneurysms are found to point more often to the left than to the right.)

The greater frequency of precordial pain in the ascending arch cases may possibly be on the basis of more frequent involvement of the coronary orifices or aortic valvular incompetency. Regarding pain referred to the head, it is of interest that one patient had a mastoidectomy because of pain

referred to this region. Some textbooks call attention to the frequency of pain referred to the left shoulder and left arm, but state that pain referred to the right upper extremity is rare. This has probably been emphasized because it suggests angina rather than aneurysm. In 28 cases of ascending arch aneurysm pain was referred to the right shoulder or arm. Pain in the left arm or shoulder occurred in 18 of the descending arch cases. In the case of the transverse segment involvement, 12 had pain referred to the right and 15 to the left upper extremity. Thus it is seen that pain radiating to the right upper extremity is by no means rare. Pain was referred to the back infrequently except in the presence of descending arch aneurysms. Of this group, 31 or about one-fifth had pain in the left back, and over one-third of the descending thoracic group also had pain at this site, due to the tendency for the sacs to point posteriorly when arising from these segments. Abdominal pain occurred in over one-third of the descending thoracic segment group and was doubtless produced by segmental radiation due to pressure upon the lower intercostal nerves.

Dyspnea occurred more often than pain in some groups. It was present in practically 65 per cent of the ascending and transverse arch aneurysm cases. One-half of the descending arch and one-third of the descending thoracic cases showed breathlessness. Dyspnea is most often due to tracheal, bronchial or pulmonary compression.

Cough appeared in roughly one-half of the cases in each group with the exception of the aneurysms of the descending thoracic aorta. Sputum accompanied cough in about one-fourth to one-fifth of the cases. Cough and sputum are manifestation of pressure on the respiratory tract causing irritation and impaired drainage of secretions. Hemoptysis was found in a few cases and was, no doubt, associated with pressure upon trachea, bronchus or lung. At times, an aneurysmal sac eroding into the respiratory tract may ooze blood for days, before rupture occurs. Again, pressure may lead to bronchiectasis with which may be noted cough, sputum and hemoptysis. The congestion due to compression of the lung may lead to blood-streaked sputum. These three symptoms associated with fever and certain physical findings have frequently led to an erroneous diagnosis of pulmonary tuberculosis.

The incidence of hoarseness was greater in the transverse and descending arch aneurysms due to their relationship to the recurrent laryngeal nerve. However, a sac of the ascending arch, pointing upward, may lead to pressure on the right laryngeal nerve, a fact not generally recognized. This will be discussed later.

Dysphagia was found most often in the transverse arch group because of the intimate relationship to and pressure upon the esophagus.

Edema of the lower extremities occurred most often in the ascending arch cases because of the greater frequency of aortic insufficiency and congestive heart failure in this group.

Tracheal compression, causing "choking spells," was found more frequently in the case of sacs of the transverse arch because of the lessened opportunity of expansion of a sac in this location without compression of adjacent structures

Vertigo, probably associated with abnormalities in the origin of the carotid arteries from the arch, appeared most often in the presence of aneurysm of transverse and ascending arch segments

Miscellaneous symptoms, not noted in the table, will be briefly enumerated. Motor and sensory disturbances in the right arm occurred in four cases of ascending arch lesions. Edema of the face and neck appeared in two cases of ascending and in four cases of transverse arch aneurysms. Pulsation and bulging of the chest wall were occasionally noted by the patients. In two ascending, one descending arch and four descending thoracic segment cases, the aneurysm was accompanied by nausea and vomiting. Hematemesis was noted in one descending arch case. Swelling of the left shoulder was noted once in the transverse arch group as was swelling of the left arm in another. Aphonia occurred once, also in this group. Paraplegia was present in two descending arch cases.

PHYSICAL SIGNS

The physical findings are summarized in table 14. If the physician will recall the directions that an expanding aneurysmal sac may take, and the anatomical structures which may be pressed upon, the symptoms and signs become clarified.

TABLE XIV
Physical Signs in Aneurysms of the Thoracic Aorta

Physical Signs	Ascend Arch (214 cases)	Trans Arch (205 cases)	Descend Arch (147 cases)	Descend Thor (30 cases)
Tracheal tug	14	22	7	1
Thrill	38	22	19	2
Diastolic shock	10	11	10	1
Pulsation, suprasternal	8	21	6	1
Pulsation, upper chest	—	4	—	—
Pulsation, rt upper chest	33	—	—	—
Pulsation, lt upper chest	—	9	14	1
Pulsation, supra-clavicular	4	—	—	—
Pulsation, neck	2	6	2	—
Pulsation, lt interscapular	—	—	17	1
Retrosternal dullness	45	62	9	—
Dullness right of sternum	26	—	—	—
Cardiac enlargement	79	64	38	—
Systolic murmur at apex	96	64	60	11
Systolic murmur at base	59	35	21	4
Diastolic murmur at base	54	33	26	4
Aortic second accentuated	25	38	26	1
Signs of cardiac failure	30	21	11	1
Fever	42	49	37	7

Tracheal tug would be expected to be produced more often by sacs of the transverse and descending segments, but from the table it may be seen that, contrary to general teaching, this sign may also be produced by ascending arch sacs. This is true because at times sacs appear on the lesser curvature of the arch, and also because they may occasionally point to the left.

Thrills are felt more easily over those sacs which point externally, and this accounts for their frequency in ascending and transverse segment aneurysms. Diastolic shock was noted about equally in the groups. Pulsation and retrosternal dullness are so obviously related to the anatomical site and direction of pointing of the sac that it seems needless to discuss this more than to call attention to the table.

The diastolic murmur of aortic incompetency was noted in 25 per cent of the cases of the ascending arch sacs, whereas it was present in 16 and 17 per cent of transverse and descending arch aneurysms respectively, and in 13 per cent of descending thoracic aneurysms. This difference is to be expected because of the site of aortitis. Of the 117 cases with aortic insufficiency, 51 had a blood pressure higher than 140 mm and of these 23 had a systolic pressure of over 160 mm.

Cardiac enlargement was recorded in 37 per cent of aneurysms of the first segment, 31 per cent of the second or transverse, and 25 per cent of the descending arch segment. These figures are probably not accurate since an error not uncommonly made in aneurysm of the aortic arch is the interpretation of downward and outward displacement of the heart as cardiac enlargement. Systolic murmurs at apex or base are difficult of interpretation from records. The former murmur is in many cases no doubt evidence of a relative mitral insufficiency accompanying a hypertrophied and dilated left ventricle. The signs of cardiac failure were found most often in the ascending arch group and associated with a regurgitant lesion of the aortic valves. Congestive heart failure is not a part of the picture of aortic aneurysm. In this series it occurred in 14 per cent of ascending, 10 per cent of transverse, 7.5 per cent of descending and 3.3 per cent of descending thoracic aortic lesions.

Because of the number of vital structures which may be compressed or distorted by an expanding aneurysmal sac a great variety of abnormal findings may be noted. (Table 15.)

In the circulatory system the most frequent effect of pressure is venous engorgement. This may be noted in the head, upper extremities and over the upper chest. Generally, it seems that sacs of the ascending and transverse arches have the most marked effect because they are so located as to most easily obstruct the venous return from head and arms. Edema of the face, neck and arms, and cyanosis were found in these two groups, as may be seen in table 12. Dilated veins of the upper chest and shoulders were also noted in the case of sacs arising from these segments of the aortic arch, in 12 to 13 per cent of each group. Occasionally one sees the most extreme

TABLE XV
Signs of Pressure Due to Aneurysmal Sacs

Signs	Ascend Arch (214 cases)	Trans Arch (205 cases)	Descend Arch (147 cases)	Descend Thor (30 cases)
Edema, face and neck	3	4	1	—
Edema, right arm	2	1	—	—
Edema, left arm	—	5	—	—
Cyanosis, head and neck	1	4	—	—
Dilated veins, upper chest	22	28	—	—
Dilated veins, rt shoulder and arm	5	—	—	—
Dilated veins, lt chest and shoulder	—	—	19	—
Trachea deviated to right	4	7	1	—
Trachea deviated to left	3	1	1	—
Respiratory stridor	9	24	10	—
Esophagus, pressure (barium)	2	9	1	1
Pupils, unequal	4	2	4	1
Pupils, left dilated	3	8	4	—
Pupils, right dilated	2	2	1	—
Vocal cords, abnormal	7	10	—	1
Vocal cords, paralysis, left	1	6	8	—
Vocal cords, paralysis, right	2	—	—	—
Pulses unequal	4	1	3	—
Pulse, right weak	3	6	—	—
Pulse, right absent	4	2	—	—
Pulse, left weak	6	4	6	1
Pulse, left absent	1	7	—	—
Paralysis right arm	2	—	—	—
Compression myelitis, paraplegia	—	—	2	—
Exophthalmus, left	—	1	—	—

and exaggerated venous pattern over the chest with blood flow downward to anastomose with dilated veins over the abdomen

Tracheal displacement must have been more common than was recorded in the case records, for in my experience it has been noted very frequently. Respiratory obstruction as made evident by stridor was met with most often in the transverse arch group, 12 per cent. Esophageal pressure as shown by barium was occasionally met with, again most often in transverse arch aneurysms.

Pupillary changes, dilatation or constriction, have been most often explained by pressure on the sympathetic chain. Wall and Walker²¹ have attempted to explain such findings on the basis of inequality of the blood pressure. They found large pupils with low blood pressure, and constricted pupils with high pressure. Anisocoria was noted by them as due to unilateral change in pressure. In 26 cases of thoracic aneurysm they found a relationship between the pupils and the pressure. The findings in this series do not agree with such an idea, since dilation of the left pupil, the most frequent abnormality, was found six times with the blood pressure equal in both arms, and found in the presence of a higher pressure on the left side, and again with higher pressure on the right. There was no relationship between blood pressure differences in the two arms and type of pupil irregularity.

Weakness or paralysis of the vocal cords was recorded as listed in the table. As would be expected from the anatomical relations of the recurrent laryngeal nerve, the vocal cord abnormalities were manifest more often on the left than on the right side. But it should be pointed out that if the sac points upward in the case of ascending arch aneurysm, there may be sufficient distortion of the right laryngeal nerve, where it loops about the subclavian artery, to lead to abnormality of the right vocal cord.

TABLE XVI
Data on Blood Pressure in Aortic Aneurysm

	Ascend Arch	Trans Arch	Descend Arch	Descend Thor
BP recorded in	126	119	77	18
Of these, both arms	76	75	36	9
BP lower on right	10	6	5	—
BP absent on right	3	1	—	—
BP lower on left	9	22	12	—
BP absent on left	1	2	—	—
BP absent, both arms	—	1	—	—

Systolic and Pulse Pressures

Systolic Pressure	Number of cases	Aortic Insuf	Pulse Pressure (within 5 mm)	Number of cases
85 to 90 mm	3	1	12	1
			20	2
90 to 110 mm	60	4	15	7
			25	27
			45	21
			55	3
			70	1
			110	1
110 to 125 mm	55	9	25	8
			35	11
			45	27
			60	8
			80	1
125 to 140 mm	89	20	30	13
			45	32
			55	27
			75	12
			90	3
140 to 180 mm	128	45	45	21
			55	25
			65	27
			85	39
			112	11
			125	1
			150	1
180 to 220 mm	21	6	35	2
			60	1
			80	9
			95	6
			120-140	3
Over 220 mm	6	1	85	3
			110	3

The blood pressure was recorded in 340 or 57 per cent of cases. Readings in both arms were made in 196 or 57.6 per cent of those having had a determination made. The blood pressure was lower in the right arm in 21, and absent in four. It was lower on the left side in 43, and absent in three. On the left it was lowered most often in the presence of transverse segment sacs. A difference of less than 15 mm. was not considered significant. Bilateral absence of demonstrable blood pressure was found once (Table 16).

In table 16 are listed also, the data in general as regards the blood pressure findings. In 128 cases, or in 38 per cent of those having blood pressure records, the systolic pressure was from 140 to 180 mm. As was noted earlier, there were 117 instances of aortic insufficiency, of which 51 had a pressure of over 140 mm. Since there were 155 cases in which the systolic pressure was over 140 mm., it is seen that aortic regurgitation was present in only one-third of the individuals with hypertension.

Pulse inequalities and differences of blood pressure in the two arms, may be explained either on the basis of pressure by the sac upon vessels as they leave the arch, or by loss of pressure in arteries arising from an aneurysmal sac. In expansion of the sac some pressure is lost. Inequality or absence of the pulse on one side was found in 8 per cent of cases with a distribution as recorded in table 15. Complete bilateral absence of pulsation was not recorded once, though in one instance the pulse was extremely weak and the blood pressure could not be recorded. Bilateral absence of the radial pulse is a rare condition. In 1930, Kampmeier and Neuman²² added a fourth such case to the only three which could be found in the literature.

Signs of pointing of an aneurysmal sac were either a localized bulging of the chest wall, with pulsation, or an expansile tumor projecting from or through the chest wall. The greatest number were found among the ascending arch group since aneurysms in this location tend to point anteriorly and to the right. There were 79 of these which constitute 37 per cent of the ascending arch aneurysms. Sixty-four or 31 per cent of the transverse arch aneurysms produced signs of a pointing sac. One-fourth of the aneurysms of the descending arch showed evidence of erosion through the chest wall, most often posteriorly. Table 17 gives in detail the sites of localized bulging or expansile tumors.

ROENTGENOLOGIC EXAMINATION

The roentgen-ray was used in the study of each of the 44 cases of aneurysm of the Vanderbilt University Hospital series, and in 447 of the Charity Hospital cases. Aneurysm was diagnosed by this means in 471 of the total 633 cases.

The accuracy of the roentgen-ray examination may be seen by a comparison of the roentgen-ray and necropsy diagnoses. Of the 165 cases in

TABLE XVII
Site of Pointing Aneurysmal Sac

	Ascend Arch (214 cases)	Trans Arch (205 cases)	Descend Arch (147 cases)	Descend Thor (30 cases)
Local bulging with pulsation				
Manubrium	—	6	—	—
Lt sterno-clavicular	—	6	—	—
Rt upper chest	17	2	—	—
Lt upper chest	—	—	10	—
Lt interscapular	—	—	2	2
Tumor, with pulsation				
Manubrium	—	18	—	—
Rt sterno-clavicular	26	12	—	—
Suprasternal	1	—	1	—
Rt upper chest	33	—	—	—
Lt upper chest	2	17	11	—
Lt neck	—	3	—	—
Lt interscapular	—	—	11	4
Lt lower chest, back	—	—	—	2

which postmortem examination was done, there were 75 in which roentgenologic study had been made. In 15 of the 71 Charity, and in 2 of the 4 Vanderbilt cases, the aortic lesion had been missed, or an error of 22.6 per cent of the cases coming to necropsy. In some of these, associated findings made the recognition of a sac impossible. For example, two of the Charity Hospital cases were diagnosed as having pleural effusion by the roentgenologist, and at necropsy this was found to be present, obscuring the aortic lesion. Similarly, massive collapse of the lung interfered with the delineation of a sac in one case. Other diagnoses in cases having aneurysmal sacs at necropsy were "hilus shadow" in one, pulmonary tuberculosis in one, tumor of left lung in one, "density in left lung" in one, pneumonia of right lower lobe in one, and a shadow was described in two but not interpreted. There were five cases in which no abnormality was noted upon roentgen-ray examination, but in which aneurysmal sacs were found at necropsy.

Roentgenologic examination showed calcification in the aneurysmal sac in 11 cases. Erosion of sternum, clavicles and ribs anteriorly was recorded a number of times. This observation generally was of no assistance to the clinician, for in all cases an expansile bulging or tumor was visible. However, erosion of one or more vertebral bodies in sacs arising from the descending arch or descending thoracic aorta was demonstrated in some cases, and such findings were of great assistance in the evaluation of symptoms or signs. In the descending arch cases, there were nine in which erosion of one or more dorsal vertebrae occurred, from the third to eighth inclusive, and in three there was erosion of the posterior arcs of one or more ribs on the left side, from the fifth to eighth inclusive. Vertebral erosion by sacs of the descending thoracic segment was seen in five cases,

with involvement of one or more vertebrae from the sixth dorsal to first lumbar inclusive. In six, the posterior arcs of one or more of the left ribs, from the seventh to twelfth inclusive, were eroded. Among the 23 cases of multiple sacs, four showed erosion of vertebrae from the third to eighth dorsal, and erosion of ribs occurred in two cases. (There was a rare case of an ascending arch sac which eroded the fourth to sixth dorsal vertebrae on the right side, found at necropsy but not noted upon roentgen-ray examination.)

CAUSE OF DEATH

Among the 633 cases of thoracic aortic aneurysm, 247 or 39 per cent died in the hospital. Necropsy was done in 165 cases or in 67 per cent of the deaths.

The causes of death, determined either clinically or at necropsy, are listed in table 18. Rupture of the aneurysmal sac occurred in 98 or in 39 per

TABLE XVIII
Cause of Death

Cause of Death	Arch	Ascend Arch	Trans Arch	Descend Arch	Descend Thor	Multiple
Rupture, lt pleura	—	1	1	6	8	1
Rupture, rt pleura	—	3	—	3	2	—
Rupture, esophagus	—	2	6	8	1	2
Rupture, trachea	—	—	3	5	—	—
Rupture, external, skin	—	2	2	—	—	—
Rupture, pericardium	—	6	—	—	—	—
Rupture, respiratory, site not known	2	—	2	5	—	—
Rupture, mediastinum	—	1	2	—	—	1
Rupture, lt bronchus	—	2	—	2	—	—
Rupture, rt bronchus	—	2	—	—	—	1
Rupture, esophagus and lt bronchus	—	—	—	—	1	—
Rupture, lt upper lobe	—	—	—	2	1	1
Rupture, rt upper lobe	—	—	—	1	—	—
Rupture, stomach	—	—	—	1	1	—
Rupture, esophagus and lt pleura	—	—	—	1	—	—
Rupture, abdominal cavity	—	—	—	1	—	—
Rupture, adhesions of lt lung	—	—	—	1	—	—
Rupture, pulmonary artery	—	—	1	—	—	—
Rupture, of abdominal aneurysm	—	—	—	1	—	—
Respiratory obstruction	3	9	25	8	—	1
Cardiac failure	2	15	5	3	2	2
Heart block	—	1	—	—	—	—
Angina pectoris	—	—	1	—	—	—
Coronary closure by pressure of aneurysmal sac	—	1	—	—	—	—
Pneumonia	—	9	9	3	—	2
Edema of lungs	—	4	1	—	—	—
Pulmonary infarct	—	—	—	1	—	1
Miliary lung abscesses	—	—	1	—	—	—
Tuberculosis of lung and pericardium	—	—	—	—	—	1
Acute nephritis	—	1	—	—	—	—
Carcinoma of prostate	—	—	—	1	—	—
Lt hemiplegia	—	2	—	—	—	—
Cause unknown	1	13	12	7	3	2
Total	8	74	71	60	19	15

cent of the deaths. Respiratory obstruction was the next most common cause of death, occurring in 46 (18 per cent), over half of which were in cases of transverse arch aneurysms. Cardiac failure as a cause appeared next with 29 (11.5 per cent) such instances. Pneumonia, probably due to bronchial obstruction, led to death in 23 cases, or 9 per cent. As may be seen in the table, a variety of causes of death appeared in isolated instances.

CASES OF MULTIPLE ANEURYSMAL SACS

More than one sac was described upon roentgen-ray examination or at necropsy in 23 cases of the series. Eight of the cases came to necropsy, and of these five had two sacs and three showed three sacs.

The duration of symptoms was no more than one month in two cases, one to three months in four cases, three to six in three cases, six to nine in three cases, and nine to 12 months in six cases. Three were of more than a year's duration, and in two no history was given.

Though no syndrome can be set up for a given combination of sacs, the clinician should not neglect to keep multiplicity of sacs in mind in the presence of symptoms inexplicable upon the basis of one sac. Incidentally, the roentgen-ray examination was fairly accurate in its diagnosis in this group.

PROGNOSIS

With comparatively few exceptions, the duration of life, after the onset of symptoms in aneurysm of the thoracic aorta, is to be measured in months. Table 19 has been compiled to show the duration of symptoms in fatal cases. The small group of multiple aneurysm cases which died have not been included for in some it was not known which sac led to the fatal issue.

TABLE XIX
Time Elapsed from Onset of Symptoms to Death

	Ascend Arch	Trans Arch	Descend Arch	Descend Thor
Less than 1 wk	—	3	1	—
2 to 4 wks, inclusive	2	6	4	—
2 to 3 mo, inclusive	10	11	10	5
4 to 6 mo, inclusive	11	17	11	3
7 to 9 mo, inclusive	11	8	7	1
10 to 12 mo, inclusive	2	1	6	—
13 to 18 mo, inclusive	7	7	4	4
19 to 24 mo, inclusive	9	5	2	2
3 yrs	6	1	3	1
4 yrs	1	—	—	1
6 yrs	1	—	1	—
14 yrs	—	1	—	—
15 yrs	1	—	—	—
"Years"	1	—	—	—
No history	12	11	11	2
Total	74	71	60	19

In arriving at averages for the various groups of cases, only those which gave a duration of symptoms of two years or less were chosen. It was felt that cases of longer standing are too few to be included for accuracy.

Generally it may be said that aneurysms of the transverse arch present the poorest prognosis as regards duration of life from the onset of symptoms. The average time elapsed from onset of symptoms to death in this group was 6.4 months. Descending arch aneurysms gave an average duration of the same length, 6.3 months, and aneurysms of the descending thoracic aorta, 8 months. These time intervals are not believed to be accurate indicators of the total duration of the lesions in these locations. Sacs of the descending arch and descending thoracic aorta are known to exist and remain asymptomatic for some time. The ascending arch aneurysms offer a slightly better prognosis. In this group the average duration of symptoms was 8.9 months. This is believed to be a possible indication of the duration of the lesion for it is in this group, as well as in the transverse arch group, that symptoms or signs become manifest early. However, it seems probable that the figures given are of little significance as regards the duration of the lesion.

Occasionally cases are found with a history of exceptionally long duration. One is inclined to discount these as mistakes in history taking or diagnosis. However, it is known that in rare instances aortic aneurysms may develop a "healed sac," by which is meant the building up of a strong wall of laminated clot, often infiltrated with calcium, which greatly retards the expansion of the sac. I have seen a patient with a calcified sac whose aneurysm had been diagnosed 13 years before, by the late P. M. Hickey, roentgenologist. In the present series one individual had experienced symptoms for 14 years and gave a history of a protruding mass for 7 years. Another patient gave a 15 year history and insisted that the protruding tumor had been present that length of time. The roentgen-ray examination revealed calcification in the sac.

SYMPTOM COMPLEXES

Aneurysm of the thoracic aorta stands second to none in interest from the standpoint of medical diagnosis. The quotation from Osler at the beginning of the paper indicates the diagnostic challenge this entity offers. Not only may aneurysm simulate many different diseases, but it also may attain immense size, and yet remain clinically silent, its presence attested to only by roentgen-ray examination or necropsy. Even after its roentgenologic revelation, a searching physical examination may still fail to elicit a single physical sign of its presence. Nevertheless, on the basis of this study, it is felt that very often, probably in most cases, either a definite or tentative diagnosis of aortic aneurysm can be made on the basis of symptoms and physical signs. If the less common symptoms and signs are noted and kept in mind and the roentgen-ray freely used, the diagnosis may be correctly arrived at even in extremely atypical instances.

The roentgen-ray examination is the most valuable aid in the diagnosis of aneurysm, but not to be used to the exclusion of the interpretation of clinical findings. It is only necessary to recall the 22 per cent of erroneous roentgen-ray diagnoses in the necropsy studies of this series. These mistakes, it must be remembered, occurred in institutions where the staffs are 'aneurysm conscious'. As has been convincingly demonstrated to me time and again by Dr Amédée Gianger, plates taken in the oblique positions, and especially in the left oblique, are of extreme value in the proper visualization of the aortic arch. These may show small aneurysms which might be missed at fluoroscopy. The examination with the fluoroscopic screen has long been considered the best means of diagnosing aneurysm because pulsations may thus be visualized. This is to be seriously questioned. It is not an infrequent occurrence to visualize a non-pulsating aneurysmal sac (organized clot) and it is extremely difficult to distinguish transmitted "pulsations" in solid tumors from the true expansile pulsation of aneurysm.

Finally, the clinician must use judgment based upon clinical findings in addition to whatever help the roentgen-ray may give. But he should not be so dependent upon the roentgen-ray that it will be allowed to exclude the diagnosis of aneurysm, else he will never have the satisfaction of seeing his clinical diagnosis of small aneurysmal sacs of the lesser curvature of the aorta established at the necropsy table. Sacs no larger than an egg at such a site may give clear-cut clinical signs but be absolutely invisible by any type of roentgen-ray study.

Symptom complexes which may be simulated by aortic aneurysm are varied and fairly numerous. It may be of interest to discuss some of these briefly.

Tuberculosis of the Lung This is probably the most frequent diagnostic error, and occurs more often, I believe, in the case of descending arch aneurysms. Sacs at this site, because they are not superficial, may exhibit no pulsation. Their location is such that they may compress the left upper lobe, or may press upon a bronchus communicating with the upper lobe. Cough, sputum and weight loss suggest the diagnosis of tuberculosis. The presence of limitation of movement of the left upper chest, an impaired percussion note, crepitant and subcrepitant râles and fever add to the confusion. Blood streaks in the sputum due to compression and stasis in the lung or from slight oozing, may occur and all but complete the clinical picture of tuberculosis. The absence of tubercle bacilli in the sputum excites suspicion and a careful roentgen-ray examination may prove the only means of diagnosing an aneurysm of the descending arch of the aorta.

Bronchiectasis Partial occlusion of a bronchus by compression is not an infrequent cause of bronchiectasis, and an aneurysmal sac may be the occluding agent. This is usually unilateral and the picture may be that of typical bronchiectasis. Stridor heard over one lobe, however, is suggestive of occlusion. The roentgen-ray may be the only means of establishing the cause of the bronchial lesion, though a small sac arising from the lesser

curvature of the arch may be so placed as to obstruct the left main bronchus and be invisible on roentgen-ray examination

Pneumoma or Delayed Resolution Similarly, obstruction in the respiratory tract may lead to the development of pneumonia. The history may be suggestive of the presence of this disease and subsequently the clinical picture may be that of delayed resolution resulting from improper drainage of secretion from the obstructed lobe.

Bronchogenic Carcinoma The diagnosis of carcinoma is suggested when a middle-aged person complains of chest pain, ineffectual cough, some dyspnea and blood-streaked sputum. An aneurysmal sac eroding a major bronchus may produce these symptoms. There may be signs of atelectasis with either carcinoma or aneurysm. In passing, it is noteworthy that the most impressive tracheal tug I have ever felt occurred in a case of carcinoma of the left bronchus which had extended through the bronchial wall to involve the aorta in a mass of malignant tissue.

Sarcoma of Lung In one of my cases there was dyspnea, cough, and edema of the right arm and shoulder. Over the right chest was widespread collateral circulation. Dullness with greatly suppressed breath sounds was present over the upper portion of the right lung. Marked pulsation in the second right interspace seemed to confirm the suspicion of aneurysm. At necropsy a huge sarcoma of the right upper lobe was found.

Laryngitis Not uncommonly the patient with aneurysm visits an otolaryngologist because of hoarseness. Examination reveals paresis or paralysis of a vocal cord. A search for intra-thoracic disease is indicated, including a careful examination for aneurysm of the aorta.

Carcinoma of the Esophagus In the case of several patients included in the series which has been presented, a tentative diagnosis of neoplasm of the esophagus had been made. Transverse and descending arch sacs may so press upon the esophagus as to lead to obstruction. Only upon fluoroscopy with or without barium in the esophagus, may the real cause of dysphagia be found.

Arthritis Pain in the shoulder, especially on the right, in ascending arch aneurysm, may by its character and aggravation on active and passive motion simulate chronic arthritis.

Tumors of Thyroid and Thymus An aneurysmal sac may so closely simulate an enlarged substernal thyroid as to lead to operation. If a thick lamellated clot is present, there is no pulsation, and the sac may be situated so that plates taken in the oblique positions will not show the aortic origin of the mass.

Mediastinal Tumors Enlargement of the mediastinal lymph nodes, as occurs in Hodgkin's disease or lympho-sarcoma, offers diagnostic difficulties, clinical as well as roentgenological. Fluoroscopy for pulsation cannot always be depended upon for differentiation. Roentgen-ray plates made in the oblique position are of great value in determining the aortic origin of mediastinal tumor.

Mediastinitis This may be syphilitic, but the character of the mediastinal shadow is not likely to be confused with a saccular lesion

Spinal Cord Tumor An aneurysmal sac eroding into the spinal canal may cause paraplegia and thus lead to the diagnosis of cord tumor Especially is this likely to occur in sacs of the descending aorta

SUMMARY

1 The historical background of aortic aneurysm has been briefly reviewed

2 From 1113 records of cases diagnosed as aortic aneurysm at the Charity and Vanderbilt University Hospitals, 633 have been selected for clinical analysis

3 The incidence of aneurysm in this country and abroad has been considered

4 Cases of saccular aneurysms of the four divisions of the thoracic aorta have been studied with respect to their clinical manifestations

5 Prognosis has been briefly considered

6 The causes of death in 247 patients have been summarized

7 Problems in the differential diagnosis of saccular aortic aneurysms have been discussed

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BIBLIOGRAPHY

- 1 ERICHSON, J E Observations on aneurism, London, 1844
- 2 MAJOR, R H Classic descriptions of disease, 1932, Chas C Thomas, Springfield, Ill
- 3 CORVISART, J N Essay on organic diseases and lesions of the heart and great vessels, (Trans) Philadelphia, 1812
- 4 BERTIN Treatise on diseases of the heart and great vessels, Philadelphia, 1833
- 5 FLINT, AUSTIN A practical treatise on the diagnosis, pathology and treatment of diseases of the heart, Philadelphia, 1859
- 6 OLIVER, W S Physical diagnosis of thoracic aneurism, Lancet, 1878, ii, 406
- 7 WELCH, F J Aortic aneurism in the army and the conditions associated with it, Lancet, 1875, ii, 769, Editorial, Ibid, 899
- 8 THOMA, R Untersuchungen uber Aneurysmen, Virchow's Arch f path Anat, 1888, cxi, 76
- 9 DOHLE, E Ueber Aortenkrankung bei Syphilitischen und deren Beziehung zur Aneurysmenbildung, Arch f klin Med, 1895, lv, 190
- 10 SCHAUDINN, F, and HOFFMANN, E Ueber Spirochaeten Befunde im Lymphdrusensaft Syphilitischer, Deutsche med Wchnschr, 1905, xxxi, 711
- 11 REUTER, K Neue Befunde von *Spirochoete pallida* im menschlichen Korper und ihre Bedeutung fur die Aetiologie der Syphilis, Ztschr f Hyg u Infektionskrankh, 1906, liv, 49
- 12 HARE, H A, and HOLDER, C H Some facts in regard to aneurysm of the aorta, Am Jr Med Sci, 1899, cxviii, 399

- 13 BOYD, L J A study of 4000 reported cases of aneurysm of the thoracic aorta, *Am Jr Med Sci*, 1924, clxviii, 654
- 14 KAMPMEIER, R H Aneurysm of the abdominal aorta a study of 73 cases, *Am Jr Med Sci*, 1936, cxlii, 97
- 15 DAHLEN, B Ueber einen Fall von Aorten-Aneurysma, mit Durchbruch in den linken Vorhof nebst einigen Bemerkungen uber Aortenaneurysma, die fibrose Aortitis in Lues, *Ztschr f klin Med*, 1907, lviii, 163
- 16 LUCKE, B, and REA, M H Studies on aneurysm I General statistical data on aneurysm, *Jr Am Med Assoc*, 1921, lxxvii, 935
- 17 OSLER, W Syphilis and aneurysm, *Brit Med Jr*, 1909, ii, 1509
- 18 LEMANN, I I Aneurysm of the thoracic aorta its incidence, diagnosis, and prognosis, *Am Jr Med Sci*, 1916, clii, 210
- 19 OSLER, W Modern medicine, 1927, Lea and Febiger, Philadelphia
- 20 WARTHIN, A S The role of syphilis in the etiology of angina pectoris, coronary arteriosclerosis and thrombosis, and of sudden cardiac death, *Am Heart Jr*, 1930, vi, 163
- 21 WALL, C, and WALKER, A An explanation of the causes of inequality of pupils in cases of thoracic aneurysm, *Lancet*, 1902, ii, 68
- 22 KAMPMEIER, R H, and NEUMAN, V F Bilateral absence of pulse in the arms and neck in aortic aneurysm, *Arch Int Med*, 1930, xlv, 513

LIVER FUNCTION IN HYPERTHYROIDISM AS DETERMINED BY THE HIPPURIC ACID TEST ^{*}

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It has long been accepted that the liver undergoes pathologic changes in hyperthyroidism. A clinical manifestation of this liver damage is the occasional presence of jaundice of the hepatic type. Cameron and Karunaratne¹ in a recent review of the subject (1935) gave Paul the credit for reporting the first case showing the association of liver injury with hyperthyroidism. He (Paul, 1865) described the case of a woman of 33 years with Graves' disease of four years' duration, who showed cirrhosis of the liver at postmortem examination. Other early observers of this relationship were Habershon (1874)² who noted in a patient with exophthalmic goiter the occurrence of progressive jaundice 10 days before death, and Eger (1880),³ Sutcliffe (1898),⁴ and Eder (1906),⁵ all of whom observed jaundice in cases of hyperthyroidism.

STRUCTURAL CHANGES IN THE LIVER

Cameron and Karunaratne collected from the literature 242 cases in which the liver showed change on postmortem examination of cases of hyperthyroidism. They added 30 cases of their own. Haban⁶ in 1933 studied 26 cases of such hepatic involvement and divided them into two groups: (1) Those with venous stasis (8 cases), and (2) those with changes independent of stasis (18 cases). In the latter group he recognized cases with fatty degeneration and infiltration, others with outstanding liver cell necrosis resembling yellow atrophy and another group of cases for which he suggested the term "cirrhosis basedowiana." Weller⁷ (1933) paid especial attention to the more chronic changes in the liver. He found what he called patchy chronic parenchymatous interlobular hepatitis in 65 per cent of his cases of exophthalmic goiter and in only 2 per cent of a control series. He noted that the changes which he found in the liver in cases of exophthalmic goiter differed from the changes seen in cirrhosis, they were irregularly distributed, many lobules appeared normal. There was also less proliferation of bile ducts. He also noted areas of necrosis still present in the parenchyma.

Rossle⁸ in 1933 divided his group of 30 cases into those showing acute or recent changes such as central and perivenous necrosis, and those with chronic changes. The changes were most marked at the edge and surface of the liver. Beaver and Pemberton⁹ in 1933 distinguished three types of histologic change in their cases: (1) acute degenerative in 91 per cent,

^{*} Read at the St. Louis meeting of the American College of Physicians, April 23, 1937.
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(2) simple atrophy in 64 per cent, and (3) subacute toxic atrophy and toxic cirrhosis in 60 per cent of the cases. The severity of the hyperthyroidism was the determining factor in the degree of pathological change.

Cameron and Karunaratne recognized three types of changes in the liver: (1) Cases with acute damage, (2) cases with evidence of progressive damage, and (3) arrested cases.

A reduction in the weight of the liver in hyperthyroidism as evidence of liver damage has been mentioned in the literature. The average liver weight of three large groups of cases (chart 1) totaling 167 cases was found

CHART I

Mean Weights of Normal Livers and Hyperthyroid Goiter Livers

		Number of Cases	Mean Liver Weight
NORMAL		50	1424 Grams
1 Rossle	30		
2 Cameron and Karunaratne	30		
3 Beaver and Pemberton	107		
Total Combined Series		167	1232 Grams

to be 1232 grams. The average weight of 50 normal livers, compiled by Boyd¹⁰ was found to be 1424 grams. The average liver weight of seven patients dying in thyroid crisis at the Lahey Clinic was 1407 grams, all were within the limits of normal.

FUNCTIONAL CHANGES IN THE LIVER

Studies of hepatic function in hyperthyroidism have been carried out by a number of investigators. Hirose¹¹ in 1912 found that patients with hyperthyroidism had a high value for alimentary galactosuria similar to that found in hepatic cirrhosis and catarrhal jaundice. In 1922 Sanger and Hun¹² studied the blood sugar curve after giving glucose to normal persons and to patients ill with hyperthyroidism. Abnormal curves were found in hyperthyroidism and attributed to a failure of the liver to store glucose.

Youmans and Warefield¹³ in 1926 studied the liver function in 44 cases of thyrotoxicosis mainly by means of the phenoltetrachlorophthalein test. They reported that 50 per cent of the patients in the entire series showed an impairment of the liver function according to the tests used. Kugelmann¹⁴ in 1930 reported the results of studies of the blood sugar curves of normal individuals and of patients with hyperthyroidism, following the feeding of levulose. He concluded that in this disease the liver had lost the capacity to transpose levulose to dextrose and to store it.

Heilmeyer¹⁵ in 1931 found the urobilin quotient elevated in three of six cases with hyperthyroidism. The power of the liver to eliminate bilirubin was impaired in each of a group of five cases. Lichtman¹⁶ found a disturbance in the oxidation of cinchophen in 16 cases of uncomplicated hyperthyroidism. This he reported as indicating moderate impairment of

the capacity of the liver cells to oxidize this substance. No evidence of severe impairment was reported and no relationship was noted between the degree of functional liver change and level of the basal metabolism, duration of disease or degree of weight loss.

Maddock, Collei, and Pedersen¹⁷ studied the liver function by means of the dye test and determination of serum bilirubin. Of 13 patients with toxic goiter, 8 or 61 per cent showed evidence of liver damage before operation. A relationship was found to exist between the severity of the disease and the degree of liver damage. Althausen and Wever¹⁸ in a recent study reported an abnormal elevation of the galactose content of the blood after the oral administration of this sugar. After thyroidectomy the galactose tolerance returned to normal.

The Takata and Ara reaction was studied by Ragins¹⁹ who found in two cases of exophthalmic goiter and in one of toxic adenoma that there was a four plus reaction, in one case of toxic adenoma a three plus reaction and in two cases of exophthalmic goiter a one plus reaction. There was a negative reaction in seven cases of exophthalmic goiter and in one of toxic adenoma.

These clinical and pathological observations conclusively demonstrate that the liver frequently suffers damage in hyperthyroidism. In addition, work by Heyd,²⁰ Boyce,²¹ and Sutton²² suggests that the hyperthermic reaction which occasionally follows operations on the bile ducts, pancreas, and thyroid is related to disturbances in the liver. Death in these cases has been termed "liver death." The typical reaction is characterized by sudden, rapid and progressive rise in the temperature during the first day after operation, falling blood pressure, rapid pulse, circulatory collapse, and coma. The temperature may reach 107 to 108 degrees within 36 to 48 hours.

With all this evidence at hand to show the increasing importance of the liver in hyperthyroidism a study was planned to investigate this subject, by a new method.

METHOD OF DETERMINATION OF LIVER FUNCTION

The liver function was determined by the hippuric acid excretion test suggested by Quick²³. The test is based on the assumption that the liver is concerned with the conjugation of benzoic acid and glycine to form hippuric acid. When a normal individual takes 6 grams of sodium benzoate by mouth, 3 grams of hippuric acid are excreted in the urine in four hours. The test has received clinical trial by Quick, Vaccaro,²⁴ Snell and Plunkett,²⁵ and Kohlstaedt and Helmer²⁶ and has been found to be a moderately satisfactory test for the determination of parenchymatous hepatic damage. The accuracy of the test compares favorably with that of other hepatic function tests. The simplicity of the test and the low cost of chemicals used in the determination are definite advantages.

MATERIAL

This study is based on the results of liver function determinations in 148 cases of clinical hyperthyroidism, all of which came to operation. Seventy-eight cases had primary hyperthyroidism permitting a subtotal thyroidectomy, 39 cases had primary hyperthyroidism requiring a two-stage operation, and 31 cases had adenomatous goiter with hyperthyroidism permitting a subtotal thyroidectomy. Liver function determinations were obtained periodically as follows. On the day after admission, on the day prior to operation (8 to 14 days being taken for preoperative treatment), and

TABLE I
Hippuric Acid Excretion in Primary Hyperthyroidism
(One stage operation)

Case	Age	Sex	Weight change pounds	Duration of disease months	Iodine prior to admission	Basal rate			Liver function			3 months check-up	
						On adm	6th day	Post-op	On adm	Pre-op	Post-op	Basal rate	Hippuric acid
1	30	F	Loss, 20	2	0	+49	+21	0	2 16	2 84	2 55		
2	37	F	Loss, 30	24	0	+41	+31	+ 7	2 22	1 93	2 65		
3	22	F	None	2	0	+18	+ 7	+22	2 62	3 20	2 28	- 5	3 97
4	32	F	Loss, 10	5	0	+44	+19	+ 6	1 07	2 32	1 32	-15	3 27
5	32	F	Loss, 19	5	0	+26	+16	- 6	2 45	2 88	2 58	- 8	3 01
6	31	F	Loss, 4	5	0	+46	+25	+19	1 75	2 45			
7	35	M	Loss, 25	12	2 wks	+26	+16		2 26	2 96	1 42	+ 3	3 16
8	31	F	Loss, 10	15	0	+44	+25	+ 9	1 13	3 08			
9	33	F	None	8	0	+49	+27		2 96	2 82	2 52	- 2	3 19
10	28	F	None	12	0	+27	+23	- 8	2 54	2 26	1 69		
11	56	M	Loss, 20	4	0	+45	+20	+18	2 45		2 16		
12	24	F	Loss, 5	12	2 wks	+25	+16		1 98	3 28	2 54		
13	39	F	Loss, 12	12	0	+17	+16		2 83	2 94		+ 5	3 13
14	42	F	Loss, 42	18	10 days	+23	+ 6	+ 5	2 03	2 07	1 83	- 9	2 67
15	36	F	Loss, 29	1	0	+32	+24		1 70	1 62	1 80		
16	20	F	Loss, 45	6	0	+24	+ 9	0	2 41		3 33		
17	26	F	None	24	0	+56	+29	+ 1	2 61	1 73		-23	2 50
18	40	F	Gain, 14	18	1 wk	+28	+17	+21	2 16		3 07		
19	32	F	Loss, 9	4	0	+24	+25	+29	2 95	2 91		0	2 99
20	23	F	Gain, 8	6	0	+29	+22		2 96		2 83		
21	45	F	None	10	0	+49	+30	+23	2 90	3 20		- 1	3 55
22	25	F	Gain, 9	12	5 mos	+68	+29	+28	2 50	2 17	2 72	+ 2	3 02
23	40	M	Loss, 50	24	2 yrs	+56	+31	+46	3 48	3 52	3 61		
24	49	F	Recent gain	36	0	+12	+13	- 5	2 56		2 33	+17	3 79
25	23	F	Gain, 10	12	0	+39	+ 9	- 6	3 03	2 92	3 03		
26	48	F	Loss, 30	8	0	+30	+16	+16		2 75	3 02	-19	4 61
27	61	F	Loss, 20	12	0	+18	+12			1 61			
28	29	F	None	18	13 mos	+22	+29		2 17				
29	52	F	None	4	0	+32	+15		2 58		0 55	- 7	2 14
30	52	F	None	2	0	+30	+14	+ 6	0 98	1 22	1 10		
31	23	F	Gain, 8	6	0	+29	+22		2 96		2 83		
32	37	F	Loss, 16	24	0	+35	+18	+15	1 77			0	3 83
33	59	F	Loss, 12	6	6 mos		+ 8	+ 7		2 84		-22	3 33
34	52	F	Loss, 25	120	9 mos	+43			1 09		0 54		
35	30	F	Loss, 15, Rest gain	7	0	+37	+14	0	2 28		2 20		
36	32	M	Gain, 8	12	0	+42	+21	+21	3 43		3 84		
37	47	F	Loss, 25	4	4 mos	+39	+18	+17	3 11		2 71		

TABLE I (Continued)

Case	Age	Sex	Weight change pounds	Duration of disease months	Iodine prior to admission	Basal rate			Liver function			3 months check up	
						On adm	6th day	Post-op	On adm	Pre-op	Post-op	Basal rate	Hip puric acid
38	29	F	Gain, 50	9	0	+30	+24			3 43	3 00		
39	48	M	Loss, 26	12	0	+37	+45	+23	2 83	3 05			
40	30	F	None	18	0	+36	+28	+16	2 99	2 12			
41	39	F	None	1	0	+33	+12			3 79			
42	25	F	Loss, 20	3	0	+56	+18			2 51			
43	50	F	Loss, 28	18	5 wks	0				2 34			
44	34	M	Loss, 19	24	0	+30	+16		3 73	3 47			
45	55	F	Loss, 2	18	1 yr	+ 2				1 69			
46	35	F	None	6	0	+16	+15			3 40			
47	24	M	Loss, 23	12	0	+40	+19	- 7	2 62	3 11			
48	48	M	Loss, 25	10	0	+29	+12		3 33				
49	32	F	Loss, 25	4	0	+48	+34			2 52			
50	23	F	Loss, 9	12	0	+56	+45		1 00	2 03	2 11		
51	16	F	Gaining	1	0	+40	+16		2 81				
52	42	F	Loss, 5	2	2 mos	+43	+30		3 03				
53	40	M	Loss, 43	5	0	+54	+30		1 84	1 38			
54	36	F	Loss, 35	12	0	+44	+20		1 59				
55	35	F	Loss, 9	6	0	+29	+20		2 09				
56	36	F	Loss, 20	4	0	+62	+22		2 18	3 18			
57	39	M	Loss, 5	18	1 wk	+19		+12	2 37				
58	57	M	Loss, 15	24	7 mos	+36	+17	-14		1 71	2 60	+ 7	3 12
59	43	M	Loss, 25	9	10 days	+12			2 39	3 34	3 56		
60	22	F	Gaining	24	6 mos	+41	+17	+16	3 73	3 41			
61	38	F	Loss, 10	12	0	+25	+14		1 65				
62	46	M	Gaining	8	0	+58	+27		1 65	2 87	2 30		
63	38	M	Loss, 30	18	0	+34	+32		2 77	3 13			
64	45	F	Loss, 12	36	0	+37	+10		2 12	1 72			
65	46	F	Loss, 12	10	0	+38	+11		2 00	1 71			
66	39	M	None	5	0	+52	+32	+ 7	1 66	2 91			
67	43	F	Loss, 20	60	0	+66	+54	+35			1 83	+ 2	3 80
68	51	F	Loss, 28	2	0	+62	+35		1 28	2 88		+33	2 77
69	33	F	Loss, 24	4	2 wks	+56	+57		2 54			-13	3 08
70	52	F	None	2	0	+24		+28	3 70				
71	19	F	Loss, 7	0 5	0		+16	+ 5		2 03			
72	42	F	Loss, 6	12	3 wks	+20	+13	+ 7	2 28		2 96		
73	53	M	Loss, 20	2 5	0	+34	+17		0 91	1 33			
74	37	F	Loss, 14	12	10 days	+13				2 59			
75	19	F	Loss, 9	8	0	+41	+19		0 65	1 90			
76	38	F	Loss, 6	1	0	+30	+39		3 53				
77	36	F	Loss, 6	3	0	+50	+42		0 04	1 43			
78	22	F	None	12	1 mo	+52	+45		1 94				

on the sixth or seventh day postoperatively. The cases requiring a two-stage operation had determinations prior to the second stage (six weeks usually elapsing between operations) and on the sixth or seventh day postoperatively. All the cases did not have the entire series of tests. Determinations were again obtained in 42 cases three months postoperatively when they returned for their usual three months metabolic check up.

RESULTS

In the group of 78 cases (table 1) whose primary hyperthyroidism was of sufficient clinical mildness to permit a subtotal thyroidectomy, the aver-

age hippuric acid excretion on admission was found to be 2.30 grams (chart 2). The average admission basal metabolic rate was plus 36 per cent. Of the entire group, only 15 per cent, i.e. 10 cases (Nos. 23, 25, 36, 37, 44, 48, 52, 60, 70, 76), had determinations above the accepted normal of three

CHART II
Hippuric Acid Excretion in Primary Hyperthyroidism
(One-stage operation)

No Cases	Average B M R %				Average Hippuric Acid Excretion in Grams			
	On Adm	On 6th Day	Postop	3 Mos Check Up	On Adm	Preop	Postop	3 Mos Check Up
78	+36	+22	+11	-3	2.30	2.55	2.39	*3.34
Percentage of normal hippuric acid determinations					15%	29%	23%	85%

* 2 cases of myxedema and 1 recurrent case not included in the determination

grams. Eight of this number had either had iodine before admission or had not suffered weight loss, and in these eight these factors were considered the basis for the normal hippuric acid excretion. After the usual preoperative period the average hippuric acid was 2.55 grams and the average basal metabolism plus 22 per cent. Although the increase in the average hippuric acid excretion was relatively small, at this point 29 per cent of the cases had normal hippuric acid excretions. Postoperatively the average hippuric acid excretion was 2.39 grams with 23 per cent of the cases having normal excretions. Three months postoperatively the average basal metabolic rate was minus 3 per cent and the average hippuric acid excretion was 3.34 grams, with 85 per cent of 20 cases now having normal excretions. In calculating this average, two cases of clinical myxedema and one case of recurrent hyperthyroidism were excluded (Nos. 17, 29, and 68).

In the group of 39 cases of primary hyperthyroidism (table 2) having the disease with sufficient clinical severity to require a two-stage operation the average basal metabolic rate was plus 54 per cent and the average hippuric acid excretion 1.88 grams (chart 3). On admission only one case (No. 37) had a normal value for the hippuric acid excretion, that happened to be in a case having an associated pregnancy. Preoperatively to the first stage the basal metabolic rate fell to an average of plus 36 per cent and the average hippuric acid excretion increased to 2.33 grams with 20 per cent of the cases now showing normal determinations. Postoperatively a slight drop occurred in the average hippuric acid excretion. Now, however, only 7 per cent had normal hippuric acid determinations. At the time of the second stage the average basal metabolic rate was plus 21 per cent with

TABLE II
Hippuric Acid Excretion in Primary Hyperthyroidism (Two stage operation)

Case	Age	Sex	Weight change, pounds	Duration of disease, months	Iodine prior to adm	First stage				Second stage				3 months check-up			
						Basal rate, per cent		Hippuric acid, in grams		Basal rate, per cent		Hippuric acid, grams					
						On adm	On 6th day	Post-op	On adm	Pre-op	Post-op	Pre-op	Post-op				
1	31	F	Gain, 6	18	6 mos	+88	+81	+32	1.41	2.93	2.12	+41	+24	2.35	2.19	-30	2.16
2	32	F	Loss, 35	10	0	+47	+30	+15	0.93	1.52	1.72	+23	+3	2.09	2.20	+5	3.00
3	27	F	None	24	0	+76	+51	+36	2.31	2.79	2.05	+20	+6	2.86	2.91	+31	0.93
4	30	F	Loss, 13	8	0	+99	+55	0	0.92	1.37	1.82	+60	+17	1.67	2.62	-4	3.16
5	36	F	Loss, 17	6	0	+44	+38	+12	1.35	2.26	2.45	+16	+4	2.52	2.62	+37	2.09
6	24	F	Loss, 20	7	0	+76	+23	+14	2.03	2.24	2.45	+42	+24	2.38	1.96		
7	60	F	Loss, 25	24	1 yr	+37	+36	+28	2.40	2.70	2.20	+11	+2	3.0	1.85		
8	55	F	Loss, 32	4	0	+66	+43	+20	1.65	2.60	2.04	-2	+4	2.55	3.10		
9	43	F	Loss, 20	3	0	+44	+43	+27	2.24	2.39	1.88	+16		2.41	1.46	-13	2.73
10	62	F	Loss, 20	4	0	+32	+37	+36	2.18	1.40	1.40	+8	+11	2.18	2.51	-6	3.08
11	46	F	Loss, 20	4	0	+15	+26	+16	1.98	1.26	1.88	+14	+12	2.38	1.64		
12	46	F	Loss, 20	8	0	+56	+24		1.28	1.58	1.99	+42	+9	1.70	3.73		
13	55	F	Loss, 40	7	1 wk	+60	+33	+34	1.31	1.73	2.26	+29	+12	2.47	3.21		
14	45	F	Loss, 3	3	3 mos	+37	+28	+31	0.76	1.73	2.09	+44	+5	1.27		+11	2.34
15	38	F	Loss, 23	9	0	+71	+53	+42	1.75	2.14	2.35	+28	-6	2.61		+5	4.00
16	53	F	Loss, 50	24	0	+42	+28	+9	2.82	3.05	2.15	-1	-6	3.38	3.13		
17	44	F	Loss, 40	2	5 days	+34	+31	+17	2.65	3.22	3.53	+36	+7	3.57			
18	16	F	Loss, 10	12	1 yr	+85	+42	+20	2.64	2.75		+14	+12	2.31			
19	54	M	Loss, 50	14	0	+63	+51	+44	2.24	1.83		+61	+33	0.97		-25	3.45
20	55	F	Loss, 80	48	0	+21	+13	+10	1.49	1.22	2.49	-2	+3	1.94			
21	33	F	Regain 5 of 20 lost	15	5 wks	+94	+43	+28	1.69	2.08	1.97	+21	+7	2.58			

TABLE II—Continued

Case	Age	Sex	Weight change, pounds	Duration of disease, months	Iodine prior to adm	First stage						Second stage				3 months check-up	
						Basal rate, per cent			Hippuric acid, in grams			Basal rate, per cent		Hippuric acid, grams		Basal rate	Hippuric acid
						On adm	On 6th day	Post-op	On adm	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op		
22	16	F	Loss, 14	12	5 wks	+33	- 4	+ 6	1 42	1 45	2 54	+ 9	- 8	2 27	3 50	-14	2 67
23	42	F	Loss, 20	6	5 mos	+79	+55	+32		3 16	2 90	+19	+10	3 50		-18	3 00
24	50	F	Loss, 14	6	4 mos	+69	+32	+18	0 84		1 94	+26	+14	2 05			
25	57	M	Loss, 45	24	6 mos	+22	+ 6	+16	2 39	3 11		0		1 88			
26	34	F	Loss, 20	10		+67	+34	+25	2 39	2 99		+26	+ 6	2 60	3 13	-13	3 00
27	54	F	Loss, 30	24	6 mos	+29	+25	+16	2 54	2 33		+25	- 6	2 62			
28	41	F	Loss, 3	48	2 yrs	+62	+38	+26				+10		3 65			
					None for 3 mos												
29	43	F	Loss, 22	30	8 mos	+53	+52	+30	2 07	3 02		+26	+20	2 84			
30	40	F	Loss, 4	36	0	+26	- 5	+11	2 28	2 27		+25	+12	3 06			
31	24	F	Loss, 20	14	0	+67	+34	+25	2 58			+15		3 86			
32	38	F	Loss, 20	3	0	+43	+34		0 89	1 83		+23		2 46			
33	48	F	Loss, 53	36	0	+65	+53	+33	1 51	3 36	2 94	+20		3 35			
34	50	F	Loss, 30	48	0	+55	+31	+28	2 29		1 92	0	+ 5			-15	3 91
35	29	M	Loss, 35	12	0	+48	+29	+20	1 48		2 78	+23	+10	2 98	3 22	- 6	3 09
36	21	M	Loss, 10	12	0	+53	+35		2 36		3 26	+20	- 6	2 62	3 13		
			Recent gain, 5														
37	34	F	Loss, 35	24	0	+62	+29	+18	3 24	2 45		+ 6		1 68		+ 2	3 23
38	33	F	Loss, 16	1	0	+49	+51		1 24	2 87		+20					
39	62	F	Loss, 48	12	0	+48	+25		2 11	1 91							

CHART III
Hippuric Acid Excretion in Primary Hyperthyroidism
(Two stage operation)

No cases	Average B M R %						Average hippuric acid excretion in grams					
	On adm	On 6th day	Postop 1st stage	Preop 2d stage	Postop 2d stage	3 mos check up	On adm	On 6th day	Postop 1st stage	Preop 2d stage	Postop 2d stage	3 mos check up
39	+54	+36	+23	+21	+7	-7	1 88	2 33	2 27	2 51	2 66	*3 12
Percentage of normal hippuric acid determinations							2%	20%	7%	22%	44%	77%

* 2 recurrent cases and 1 case of myxedema not included in the determination

the average hippuric acid excretion 2 51 grams At this point 22 per cent of the cases had normal tests Postoperatively the average hippuric acid excretion was 2 66 grams with 44 per cent of the cases having normal tests At the three months check up in 16 cases the average basal metabolism was minus 7 per cent with the average hippuric acid excretion 3 12 grams In calculating the average in this group of 16 cases, two cases of recurrent hyperthyroidism (4, 6) and one case of myxedema (2) were excluded At this time 77 per cent of the cases had normal determinations This average figure is affected by the presence of two cases (Nos 14, 22) who had weights less than 100 pounds being 73 and 91 pounds respectively, and where the normal excretion would hardly be expected to be 3 grams

In the 31 cases of adenomatous goiter with hyperthyroidism (table 3) the average basal metabolic rate on admission was plus 36 per cent and the average hippuric acid excretion 2 27 grams (chart 4) Seven cases, or 23 per cent, had normal hippuric acid excretion (Nos 6, 8, 19, 22, 24, 29, 30) In this group of seven cases, five had not lost weight and two had taken iodine for long periods before admission The average basal metabolic rate was plus 24 per cent and the average hippuric acid excretion 2 33 grams preoperatively Eleven per cent of the cases had normal hippuric acid excretion at this point Postoperatively, the hippuric acid excretion was 2 36 grams with 16 per cent of the cases being normal At the three months' check up six cases had an average metabolic rate of minus 5 per cent with the hippuric acid excretion 3 34 grams

A comparative study of these groups of cases (figure 1) shows that a close relationship exists between the level of the basal metabolism and the hippuric acid excretion The cases with primary hyperthyroidism permitting a subtotal thyroidectomy had an average basal metabolism equal to the group of adenomatous goiters The average admission hippuric acid excretion in the two groups was practically the same being 2 30 and 2 27 grams The group of primary hyperthyroidism requiring the two stage operation had a higher average basal metabolism, plus 54 per cent, and a lower average hippuric acid excretion, 1 88 grams

TABLE III
Hippuric Acid Excretion in Adenomatous Goiter with Hyperthyroidism
(One-stage operation)

Case	Age	Sex	Weight change pounds	Duration of disease years	Iodine prior to admission	Basal rate per cent			Liver function in grams			3 months check-up	
						On adm	On 6th day	6th day postop	On adm	Pre-op	Post-op	Basal rate	Hippuric acid
1	47	F	Loss, 17	1 5	0	+33	+27	+13	2 30	2 95			
2	61	F	Loss, 20	3	0	+44	+27	+32	2 11	2 01	2 13	- 3	3 10
3	53	F	Loss, 12	0 33	0	+51	+28	+34	1 93	2 51		-10	2 56
4	33	F	Loss, 10	0 5	0	+17	+14	+10	2 26	2 32	2 87		
5	30	F	Loss, 30	3	0	+33	+15	+19	2 31	2 79			
6	54	F	None	2	0	+38	+29	+52	3 60		3 47		
7	52	F	Loss, 15 Regain, 5	2	0	+40	+28	+30	0 89	1 97	1 85	- 4	3 03
8	52	F	None	0 25	0	+19		+ 7	3 45		3 56		
9	45	M	Loss, 15	4 2	0	+70	+39	+23	2 89	2 99	1 42	- 8	3 69
10	60	F	Loss, 10	2	2 mos	+21	+11	+18	1 97	1 79	2 12		
11	66	F	Loss, 20	6	0	+28	+10		0 54	Weight 79 pounds Postoperative death			
12	43	F	Gain, 4	1	8 mos	+63	+37	+25	2 33	2 71		-10	3 43
13	52	F	None	2	0	+46	+32	+12	1 46	2 57			
14	57	F	Loss, 15	1	4 mos	+40	+38		2 11	1 79			
15	47	F	Loss, 26	2	0	+60	+32	+23	2 44	1 05	2 84	- 8	4 26
16	57	M	Loss, 70	6	0	+41	+24	- 4	1 11	1 30	1 58		
17	63	F	Loss, 26	0 33	0	+50	+37	+26		2 45			
18	51	F	None	2	0	+19	+14	+14	2 58				
19	57	F	Loss, 40	0 33	0	+51	+35		3 49	3 77			
20	54	F	Loss, 18	0 5	3 wks	+18	+14		1 20				
21	40	F	Loss, 13	1	0	+22	+ 5		0 92	1 58	1 64		
22	57	F	Loss, 5	0 75	7 mos	+26	+ 9		3 65				
23	49	F	Loss, 28	0 66	3 mos	+54	+44	+ 8	2 30				
24	37	F	Gain, 5	3	0	+28	+ 9	+ 9	3 77				
25	41	F	Loss, 20	2	0	+39	+22		2 14	2 48			
26	43	F	Loss, 7	1	0	+12			1 81				
27	57	F	Loss, 8	4	0	+38	+24		1 48				
28	52	F	Gain, 4	2	0	+24			2 71	3 11	2 85		
29	62	F	Loss, 40	3	5 mos	+21	+16	+19	3 18		2 40		
30	47	F	None	0 33	0	+50	+26		3 02				
31	61	F	None	0 75	0	+19			2 18				

CHART IV
Hippuric Acid Excretion in Adenomatous Goiter with Hyperthyroidism
(One-stage operation)

No Cases	Average B M R %				Average Hippuric Acid Excretion in Grams			
	On Adm	On 6th Day	Postop	3 Mos Check Up	On Adm	Preop	Postop	3 Mos Check Up
31	+36	+24	+20	-6	2 27	2 33	2 36	3 34
Percentage of normal hippuric acid determinations					23%	11%	16%	83%

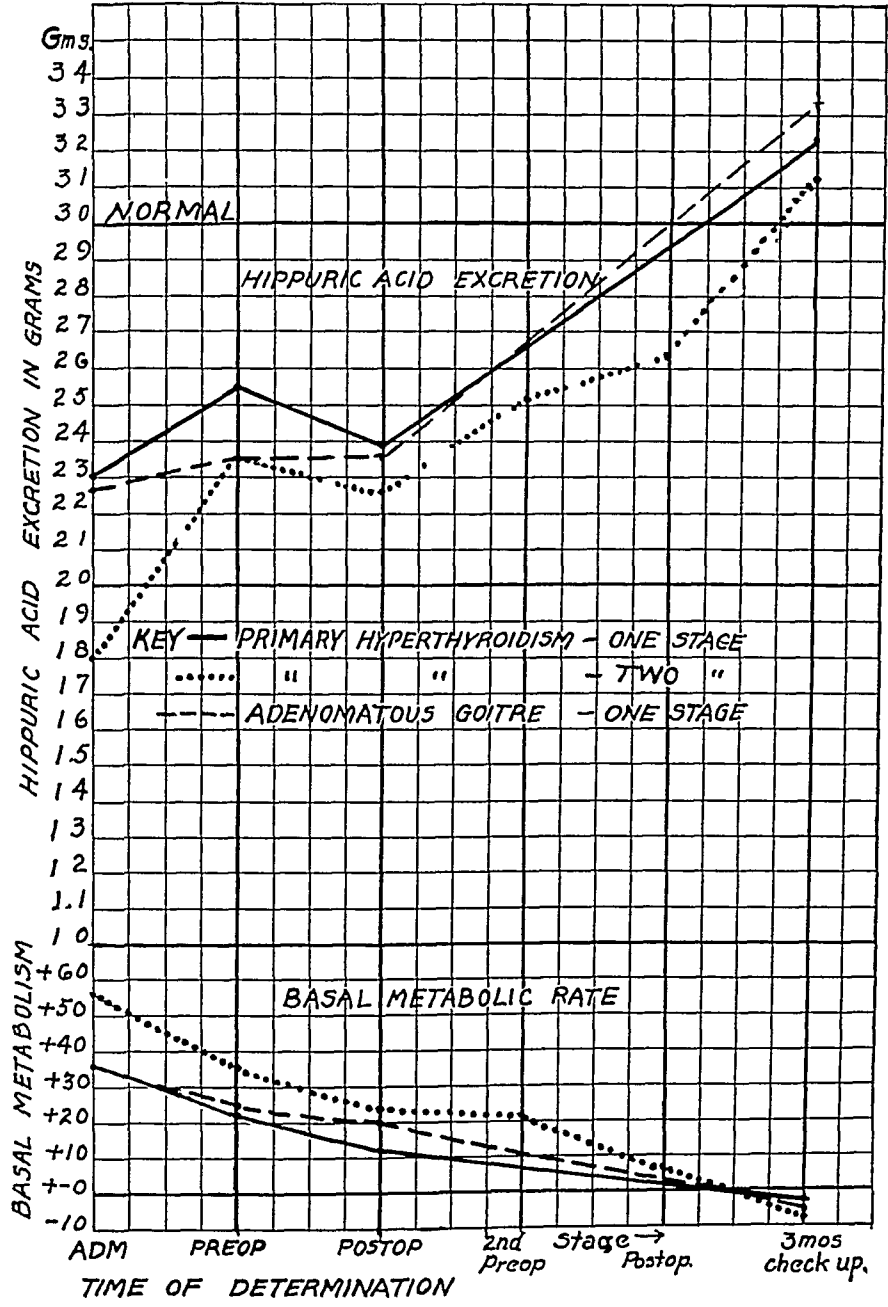


FIG 1 Hippuric acid excretion and basal metabolism in hyperthyroidism

As shown, the trend of the average hippuric acid during preoperative treatment in the cases of primary hyperthyroidism is upward. However, the group of adenomatous goiters have a fairly constant excretion. A slight postoperative drop occurred in the average hippuric excretion in the two groups of cases with primary hyperthyroidism. The hippuric acid excretion in the two stage cases showed a gradual increase at the time of the second operation with a continued rise postoperatively. All the groups then went to a normal average hippuric acid excretion at the time of the three months' check up. The trend of the average basal metabolic rate was downward in all the groups.

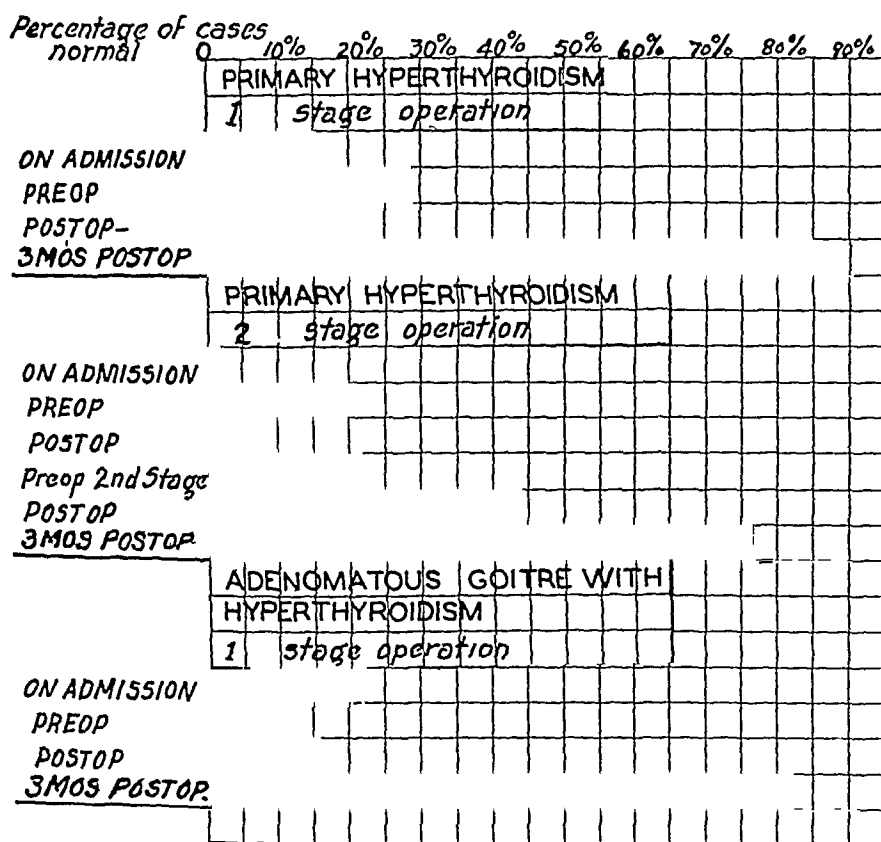


FIG 2 Cases of hyperthyroidism with normal hippuric acid excretion

When a comparison is made with the percentage of cases showing normal excretion in the three groups during the period of study certain features are worthy of mention (Figure 2). Only 2 per cent of the severe cases requiring a two stage operation had normal hippuric excretion on admission, as compared to 15 per cent in the group of lesser clinical severity having a subtotal thyroidectomy, and to 23 per cent in the group of adenomatous goiters. A rise in hippuric acid excretion occurred preoperatively in the groups of cases of primary hyperthyroidism but a slight drop appeared at

this stage in the adenomatous group Postoperatively a drop occurred in the two stage group suggesting the effect of operative strain on the liver in these more toxic cases A high per cent of normals occurred in all the groups at the time of the three months' check up

It was found that the duration of the hyperthyroidism was not a potent factor in determining the degree of liver function reduction as shown in figure 3 Patients having acute hyperthyroidism were found to develop degrees of liver impairment in a few months where patients with milder types had little change even after years This observation is corroborated by the fact that, whereas the average duration of the disease in the group of cases of primary hyperthyroidism having a subtotal thyroidectomy was

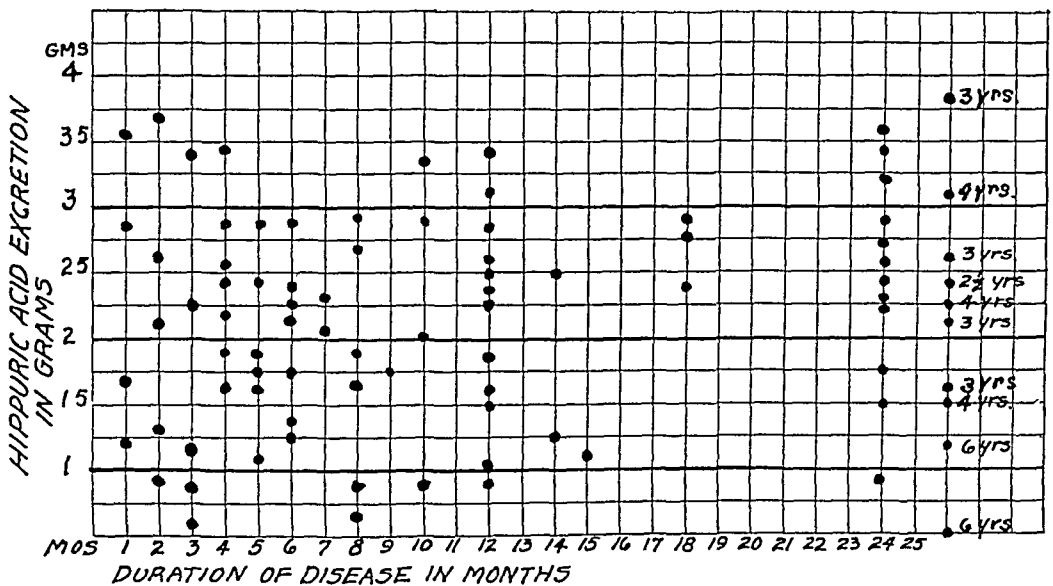


FIG 3 Duration of *hyperthyroidism in relation to hippuric acid excretion
* No iodine prior to admission

10 months and in the group of adenomatous goiters 21 months, the hippuric acid excretion in both these groups was found to be the same

In an attempt to relate the postoperative temperature and pulse response to the degree of functional impairment of the liver a comparison was made of the postoperative clinical course and the level of the hippuric acid excretion A series of cases was selected at random having hippuric acid excretion of varying amounts, below one gram, between 1 and 2 grams, between 2 and 3 grams, and over 3 grams (Figures 4, 5, 6, 7, 8) No apparent uniformity was found to occur in the postoperative temperature and pulse response in the various hippuric acid levels A typical crisis reaction did occur in a case having a hippuric acid excretion below 1 gram, but severe reactions occurred in cases having excretions even above the

normal of 3 grams One case is of particular interest (figure 6) in that with the same level of the hippuric acid excretion prior to the first and second operation she had a normal response after the first operation and suffered a severe reaction after the second Thus it is shown that the type

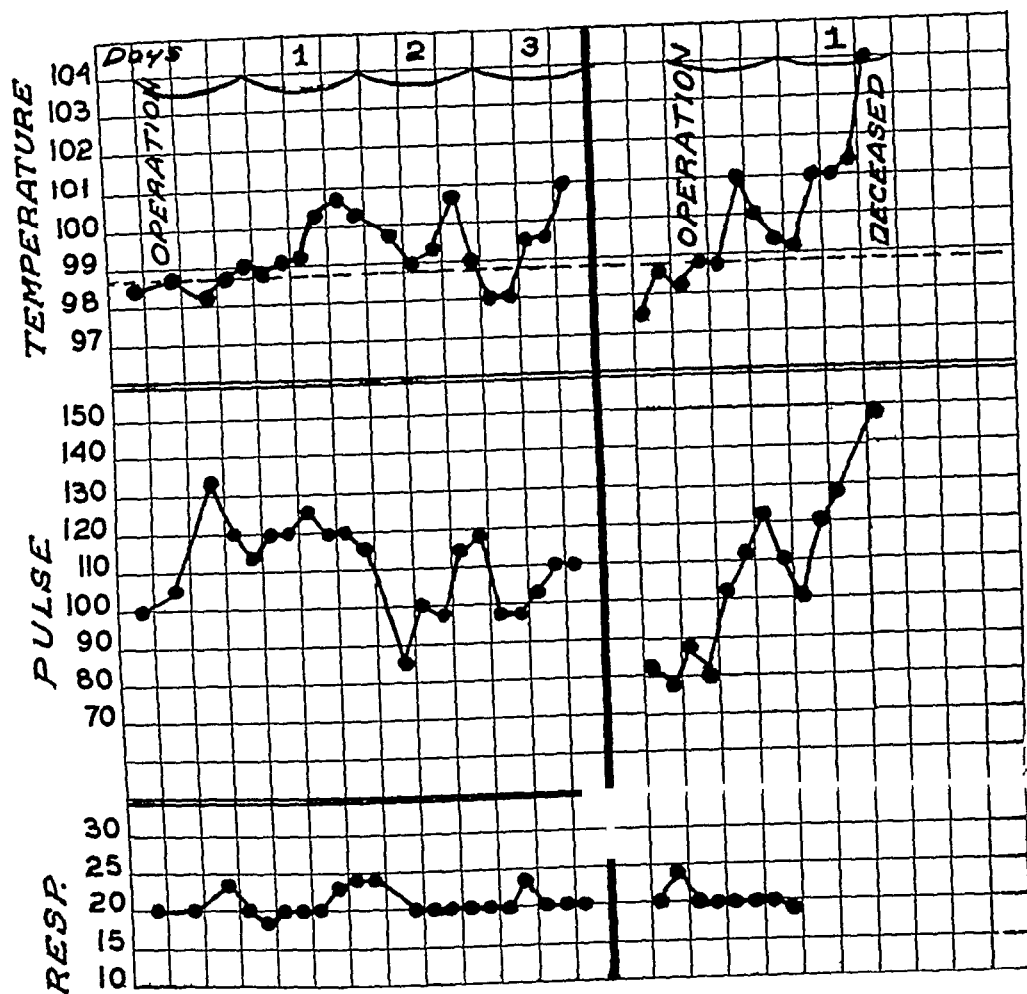


FIG 4 Postoperative clinical response—hippuric acid excretion less than 1 gram

Mrs M O Age 50
Adm B M R + 69
Dur 6 months
Wt loss—14 lbs
Rt Hemithyroidectomy
Hippuric Acid } 84 gram
Excretion } 43 gram

Mrs A J Age 66
B M R + 28
Dur 6 years
Wt loss—20 lbs
Rt Hemithyroidectomy
Hippuric Acid } 54 gram
Excretion } 67 gram

of postoperative response cannot be predicted from the level of the hippuric acid excretion This tends to cast a shadow of doubt on the opinion that the thyroid crisis reaction is entirely on the basis of the liver function impairment

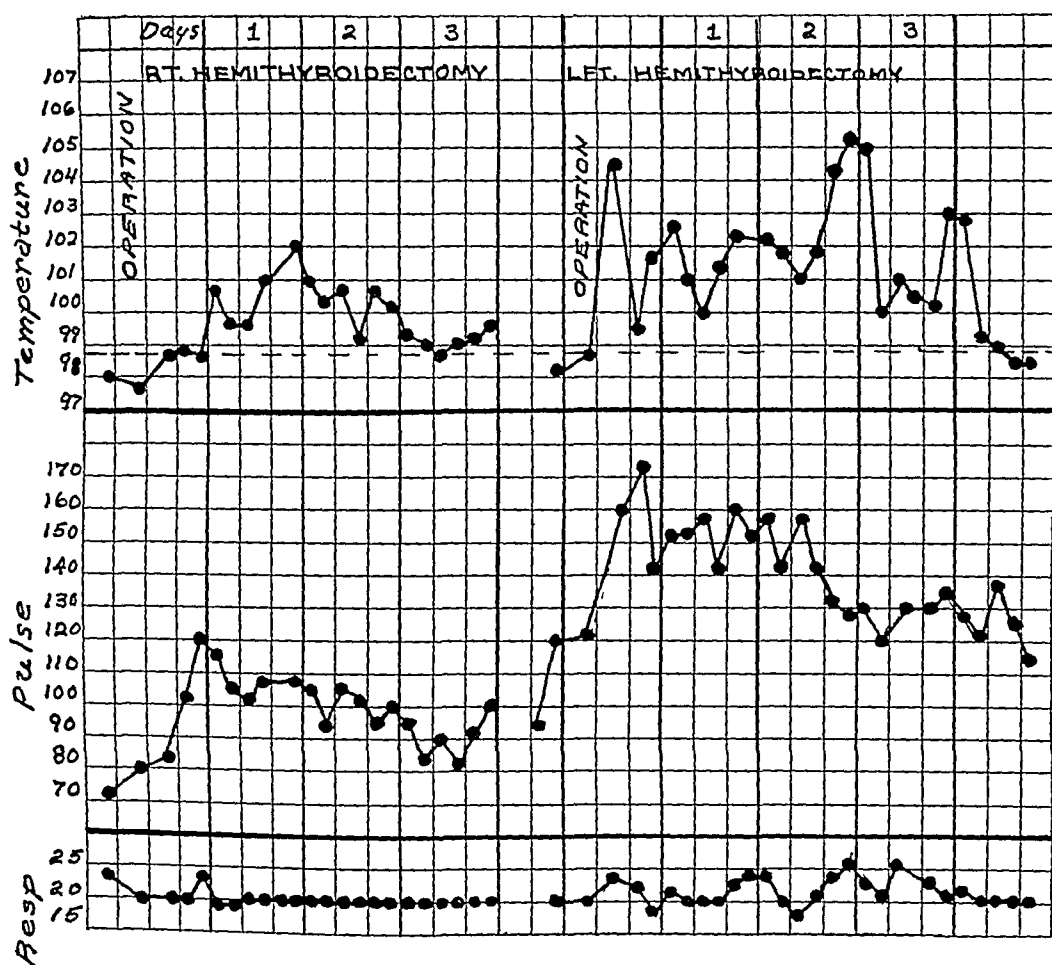


FIG 6 Postoperative clinical response—hippuric acid between 2 and 3 grams

Miss A L Age 24
 B M R 1st Stage + 76 2d Stage + 44
 Duration 7 Mos
 Wt loss—20 lbs
 Liver Function } 1st Adm } 2d Adm
 } 2 03 Gm } 2 38 Gm
 } 2 24 Gm }

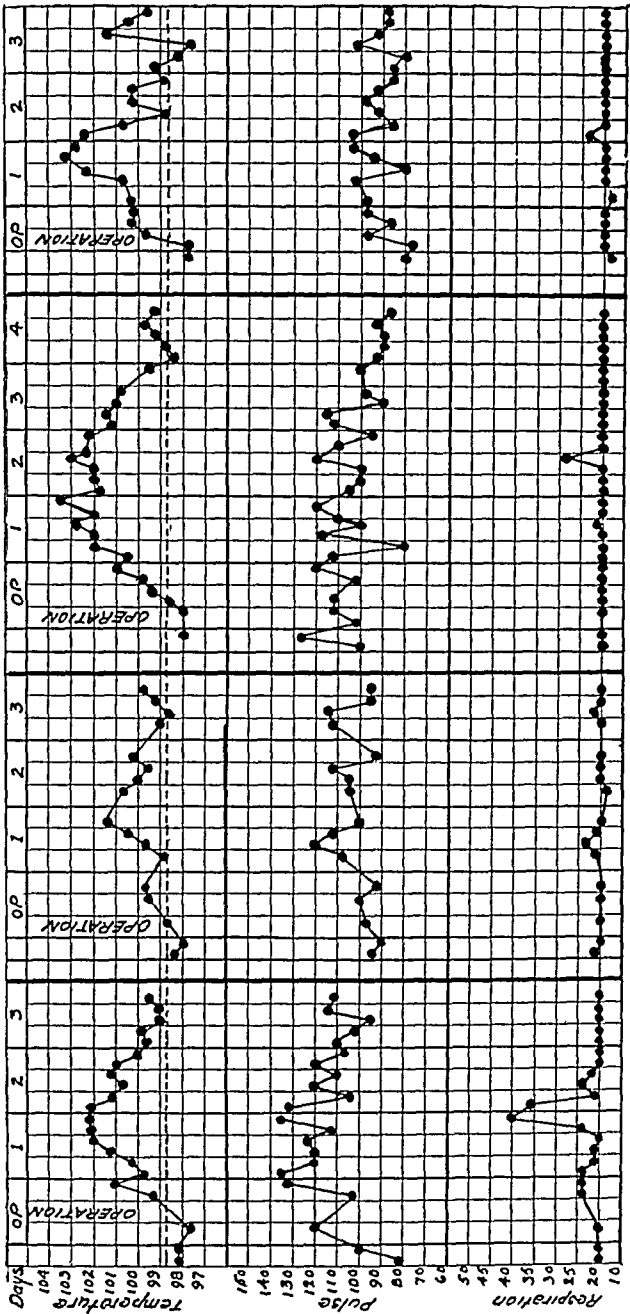


Fig 7 Postoperative clinical response—hippuric acid excretion between 2 and 3 grams

Mrs G H Age 23
B M R + 29
Dur 6 months
Wt loss—None
Subtotal Thyroidectomy
Liver } 296 Gm
Function } 283 Gm

Miss L B Age 30
B M R + 49
Dur 2 months
Wt loss—20 lbs
Subtotal Thyroidectomy
Liver } 216 Gm
Function } 284 Gm

Mr J K Age 48
B M R + 51
Dur 1 year
Wt loss—26 lbs
Subtotal Thyroidectomy
Liver } 283 Gm
Function } 305 Gm

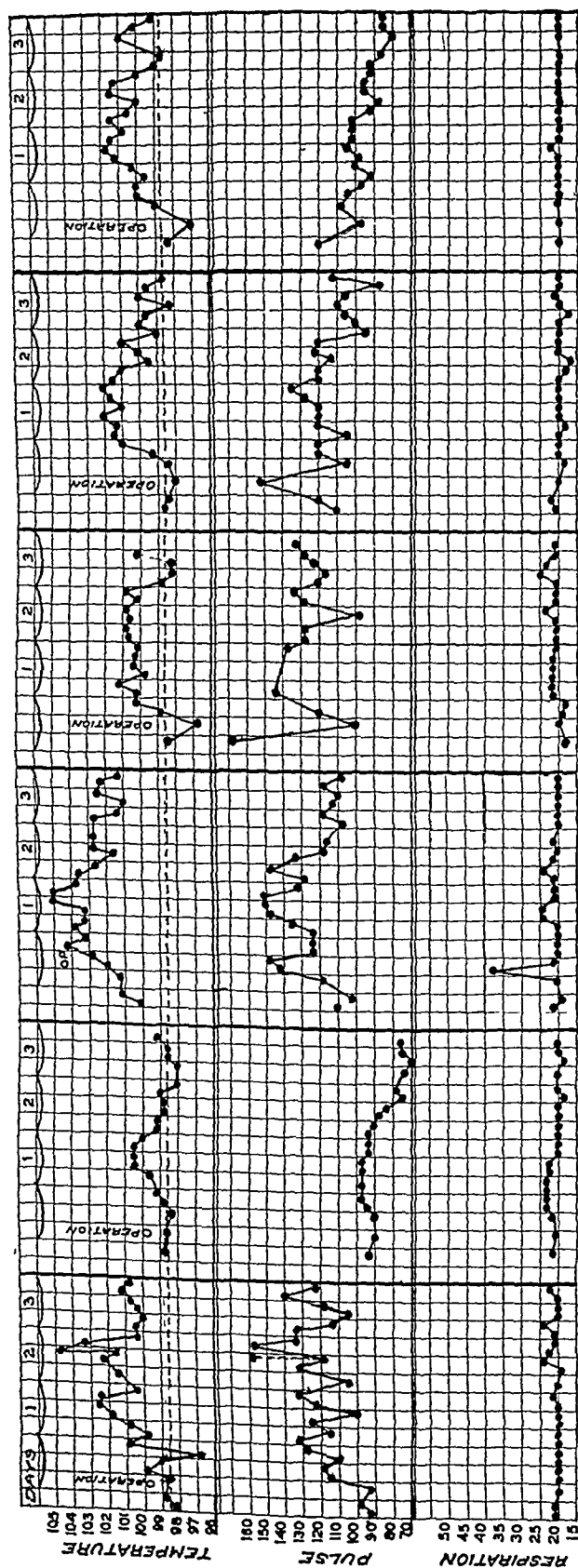


FIG 8 Postoperative clinical response—hippuric acid excretion over 3 grams

Mrs R N Age 29
 BM R + 30
 Dur 9 months
 Gaining weight
 Subtotal Thyroidectomy
 Liver } 343 Gm
 Function } 300 Gm

Mrs I L Age 39
 BM R + 45
 Dur 1 month
 Wt loss—None
 Subtotal Thyroidectomy
 Liver } 379 Gm
 Function }

Mr R M Age 32
 BM R + 73
 Dur 6 months
 Wt loss—50 lbs
 Rt Hemithyroidectomy
 Liver } 333 Gm
 Function } 378 Gm

Mr R C Age 36
 BM R + 40
 Dur 1 year
 Wt loss—25 lbs
 Bilateral Pole Ligation
 Liver } 314 Gm
 Function } 343 Gm

HIPPURIC ACID EXCRETION, BLOOD CHOLESTEROL AND SERUM PROTEIN

Hurxthal,²⁷ Adler²⁸ and others have reported that the blood cholesterol is reduced in hyperthyroidism. A return toward normal occurs after pre-operative treatment and especially after thyroidectomy. Epstein and Greenspan²⁹ more recently have attributed the cholesterol reduction to parenchymatous liver change. It is therefore to be assumed that in hyperthyroidism the lowering of the blood cholesterol is related to liver impairment. It has also been accepted that in diseases of the liver a lowering occurs in the serum protein of the blood with an alteration of the albumin globulin ratio. A comparative study of the hippuric acid excretion, blood cholesterol, and serum protein was carried out in 19 cases (table 4). In

TABLE IV
Blood Cholesterol in Hyperthyroidism*
Hippuric acid excretion and serum protein

Case	Hippuric acid in grams		Blood cholesterol, mg		Serum protein, gm	
	Admission	Preoperative	Admission	Preoperative	Admission	Preoperative
1	2.16	2.84	127	176	6.3	6.0
2	2.22	1.93	154	188	7.6	6.6
3	0.92	1.37	97	170	6.0	6.5
4	2.83	2.94	138	186	6.8	6.6
5	2.62	3.20	136	161	6.1	7.3
6	1.07	2.32	232	220	6.4	7.6
7	2.31	2.79	121	161	6.4	6.1
8	2.36	2.96	173	137	7.3	8.2
9	2.45	2.88	140	171	6.3	6.6
10	1.35	1.72	104	142	5.3	5.4
11	2.64	3.04	109	169	7.2	6.9
12†	2.30	2.95	158	196	6.0	8.8
13	2.55	2.91	165	177	6.7	7.2
14†	2.11	2.01	161	192	6.4	6.8
15	1.65	2.60	176	190	6.3	4.9
16	2.03	2.24	133	182	6.4	5.9
17†	1.93	2.51	150	225	6.5	6.9
18	1.98	1.26	183	232	6.8	6.4
19†	2.31	2.79	201	203	6.7	6.7
Average	2.06	2.48 (20%)	150	183 (20%)	6.5	6.7
Increase		0.16		17		1.0
Decrease		0.3		2		0.9

* No iodine prior to admission

† Cases having adenomatous goiter with hyperthyroidism, all the others primary hyperthyroidism

this group of cases the average admission hippuric acid excretion was 2.06 grams, cholesterol 150 mg, and serum protein 6.5 gm (chart 5). Pre-operatively the hippuric acid excretion and the blood cholesterol showed increases of 20 per cent. In 16 cases the hippuric acid excretion increased and in 17 cases the blood cholesterol increased. An apparent relationship was found to exist between the level of the hippuric acid and the blood

CHART V

Cholesterol Study of Hippuric Acid Excretion—Blood Cholesterol and Total Serum Protein

No Cases	Average Hippuric Acid in Grams		Average Blood Cholesterol in Mg		Average Total Serum Protein in gm	
	On Adm	Preop	On Adm	Preop	On Adm	Preop
19	2 06	2 48	150	183	6 5	6 7
Percentage increase		20%		20%		

cholesterol However, no relationship was found to exist between the level of the hippuric acid and the level of the total serum protein (figure 9) The average total protein on admission was found to be 6 5 gm Pre-operatively the determination was practically the same, being 6 7 gm Macrocytic anemia due to liver disease did not occur in the cases studied

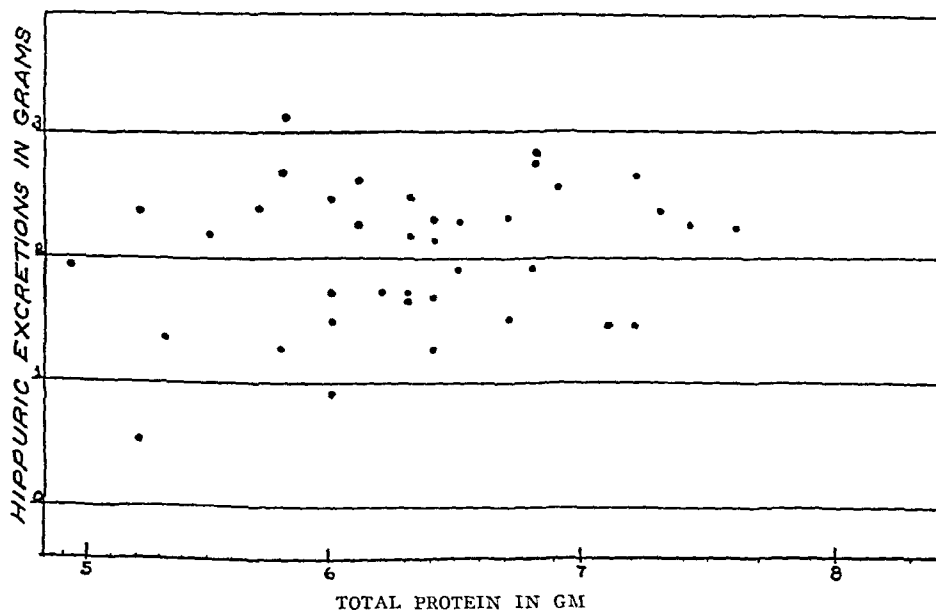


FIG 9 Hippuric acid excretion and total serum protein

Mr H E Age 40
 B M R + 56
 Dur 2 years
 Wt loss—50 lbs
 Subtotal Thyroidectomy
 Liver } 3 48 Gm
 Function } 3 55 Gm
 } 3 52 Gm

Mr W H Age 32
 B M R + 42
 Dur 1 year
 Wt loss—30 lbs Regained 8
 Subtotal Thyroidectomy
 Liver } 3 43 Gm
 Function } 3 84 Gm

APPARENT EFFECT OF DIGITALIS ON HIPPURIC ACID EXCRETION

In the course of the study certain cases were found to have hippuric acid excretions which were exceptionally low for the degree of severity of

their thyroid disease. Others showed substantial drops in the hippuric acid excretion following preoperative treatment. In seeking an explanation for these occurrences it was found that these cases had received digitalis prior to admission or during the course of preoperative treatment. Cardiac complications such as pulse irregularities and myocardial failure had indicated the use of the medication. One case after seven days of digitalis had a drop in the hippuric acid excretion from 1.77 grams to 0.57 gram, one case after 26 days of digitalis had a drop from 1.09 grams to 0.54 gram, one case after 7 days of digitalis had a drop from 1.33 grams to 0.88 gram. Another case demonstrated this drop on two occasions, the first time from 3.10 grams to 0.77 gram after seven days of digitalis and again from 2.80 grams to 1.46 grams after 10 days of digitalis. These observations suggest that in hyperthyroidism digitalis is toxic to the liver.

ATTEMPTS AT ALTERING THE HIPPURIC ACID EXCRETION

Having shown that the function of the liver is reduced in hyperthyroidism attempts at enhancing the return to normal preoperatively were instituted. A number of methods were tried, each one having a suggestive clinical reason for its employment.

As a high carbohydrate-low fat diet is the accepted treatment for liver disease 17 cases were placed on this regime. The usual hospital diet for patients with hyperthyroidism is high in calories and vitamins with an average content made up of carbohydrate 377 grams, protein 119 grams, and fat 200 grams, with a caloric value of 3784 calories. The diet employed had individual variations ranging in carbohydrate from 395 grams to 1099 grams and in fat from 22 grams to 60 grams, with a caloric value from 2700 to 5000 calories. The protein remained between 60 to 80 grams. The average hippuric acid excretion for the group on admission was 1.77 grams and after approximately 10 days on the diet 2.40 grams with 13 cases showing striking increases in the hippuric acid. Although normal determinations were not obtained after such a forced carbohydrate feeding it seems logical to suppose that this is the most suitable diet for patients with this disease.

Glycine given in 15 grams daily doses returned the hippuric acid excretion to normal in three cases. One of these cases had on admission a hippuric acid excretion of 0.92 gram. The effect of glycine on the hippuric acid excretion has been reported by Quick. The placing of readily available glycine in the system by such large doses suggests a possible source of error for the test as the liver may not be entirely involved in the conjugation of the benzoic acid to hippuric acid, other factors may play a part.

CONCLUSIONS

1. Reduction in the liver function as shown by the hippuric acid excretion test was observed in a high proportion of cases of hyperthyroidism.

On admission only 18 cases out of 148 cases had a normal response to the test

2 The degree of change in liver function is in direct relation to the severity of the hyperthyroidism, as determined by the basal metabolic rate and the clinical opinion as to the necessity for a one or a two stage operation

3 No apparent correlation was found to exist between the liver function and the duration of the hyperthyroidism. The absence of weight loss or a history of previous iodine administration was usually noted in conjunction with a normal admission liver function test

4 Improvement in liver function occurred during preoperative treatment in the cases with primary hyperthyroidism. No apparent change was noted in adenomatous goiter with hyperthyroidism

5 Normal liver function was found in a high per cent of cases three months postoperative, indicating that the liver damage from hyperthyroidism is rarely permanent

6 No apparent relationship was demonstrated between the level of the liver function and the degree of postoperative pulse and temperature response

7 A close relationship was found to exist between the blood cholesterol and the hippuric acid excretion

8 The use of a high carbohydrate diet apparently improved the liver function as indicated by increased hippuric acid excretion

9 As the liver plays a vital rôle in the general body metabolism the change which occurs in its function in hyperthyroidism must represent a serious physiological handicap to the patient

REFERENCES

- 1 CAMERON, G R, and KARUNARATNE, W A E Liver changes in exophthalmic goitre, *Jr Path and Bact*, 1935, xli, 267-282
- 2 HABERSHON, S O Exophthalmic goitre heart disease jaundice, death (Notes by W E DRING), *Lancet*, 1874, i, 510
- 3 EGER Beitrag zur Pathologie des Morbus Basedowi, *Deutsch med Wchnschr*, 1880, vi, 153-157
- 4 SUTCLIFF, E H An extraordinarily acute case of Graves' disease, *Lancet*, 1898, i, 717
- 5 EDER, M D Three cases of jaundice occurring in persons suffering from exophthalmic goitre, *Lancet*, 1906, i, 1758
- 6 HABAN, G Über die Leberveränderungen bei Morbus Basedowi mit besonderer Berücksichtigung der Lebercirrhose, *Beitr z path Anat u z Allgem Path*, 1933, xxi, 88-110
- 7 WELLER, C V Hepatic pathology in exophthalmic goiter, *ANN INT MED*, 1933, vii, 543-560
- 8 ROSSLE, R Über die Veränderungen der Leber bei der Basedowschen Krankheit und ihre Bedeutung für die Entstehung anderer Organsklerosen, *Virchow's Arch*, 1933, ccxci, 1-46
- 9 BEAVER, D C, and PEMBERTON, J DEJ The pathologic anatomy of the liver in exophthalmic goiter, *ANN INT MED*, 1933, vii, 687-708
- 10 BOYD, E Normal variability in weight of the adult human liver and spleen, *Arch Path*, 1933, xvi, 350-372

- 11 HIROSE, M Über die alimentäre Galaktosurie bei Leberkrankheiten und Neurosen, Deutsch med Wchnschr, 1912, *xxxviii*, 1414-1416
- 12 SANGER, B J, and HUN, E G Glucose mobilization rate in hyperthyroidism, Arch Int Med, 1922, *xx*, 397-406
- 13 YOUMANS, J B, and WAREFIELD, L M Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency, Arch Int Med, 1926, *xxvii*, 1-17
- 14 KUGELMANN, B Über Störungen in Kohlehydratstoffwechsel beim Morbus Basedow, Klin Wchnschr, 1930, *ix*, 1533-1534
- 15 HEILMEYER, L Blutfarbstoffwechselstudien 3 Mitteilung Blutmauserung und Leberfunktion beim Morbus Basedow, Deutsch Arch f klin Med, 1931, *clxxi*, 515-528
- 16 LICHTMAN, S S Liver function in hyperthyroidism, Arch Int Med, 1932, *i*, 721-729
- 17 MADDOCK, W G, COLLIER, F A, and PEDERSEN, S Thyroid crisis its relation to liver function and adrenalin, West Jr Surg, 1936, *xliv*, 513-521
- 18 ALTHAUSEN, T L, and WEVER, G K Galactose tolerance in hyperthyroidism, J Clin Invest, 1937, *vi*, 257-259
- 19 RAGINS, A B Value of Takata and Ara reaction as diagnostic and prognostic aid in cirrhosis of liver, Jr Lab and Clin Med, 1935, *xx*, 902-913
- 20 HEYD, C G Liver and its relation to chronic abdominal infection, Ann Surg, 1924, *lxxix*, 55-77
- 21 BOYCE, F F The so-called liver death syndrome (Editorial), Surg, Gynec and Obst, 1935, *lxi*, 122-123
- 22 SUTTON, J E, JR High temperature liver death syndrome, Proc Soc Exper Biol and Med, 1935, *xxxii*, 712-713 Acute postoperative necrosis of liver (so-called high temperature liver death syndrome), Am Jr Med Sci, 1936, *xcii*, 219-224
- 23 QUICK, A J Synthesis of hippuric acid, new test of liver function, Am Jr Med Sci, 1933, *clxxv*, 630-635
- 24 VACCARO, P F Synthesis of hippuric acid Its value in detecting hepatic damage secondary to diseases of extrahepatic biliary system, Surg, Gynec and Obst, 1935, *lxi*, 36-42
- 25 SNELL, A M, and PLUNKETT, J E Hippuric acid test for hepatic function Its relation to other tests in general use, Am Jr Digest Dis and Nutr, 1936, *ii*, 716-772
- 26 KOHLSTAEDT, K G, and HELMER, O M Study of hippuric acid excretion as test of hepatic function, Am Jr Digest Dis and Nutr, 1936, *iii*, 459-466
- 27 HURVITZ, L M Hyperthyroidism, Surg Clin N Am, 1936, *vi*, 1505-1508
- 28 ADLER, A (Leipzig), and LEMMEL, H Zur feineren Diagnostik der Leberkrankheiten Cholesterin und Cholesterin-ester im Blute Leberkranker, Deutsch Arch f klin Med, 1928, *clviii*, 173-213
- 29 EPSTEIN, E Z, and GREENSPAN, E B Clinical significance of cholesterol partition of blood plasma in hepatic and in biliary diseases, Arch Int Med, 1936, *lvi*, 860-890

GONORRHEAL ENDOCARDITIS; A REPORT OF THREE CASES, ONE TREATED WITH FEVER THERAPY¹

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THERE have been numerous reports of the treatment of gonorrheal infections with fever therapy during the past few years. These reports have dealt mainly with cases of gonorrheal arthritis, though gonorrheal pelvic inflammatory disease and other local manifestations of the infection also have been treated successfully by heat therapy. We wish to report a case of gonorrheal endocarditis treated by fever therapy unsuccessfully, and also to report two cases of gonorrheal endocarditis not previously reported. Freund and Anderson reported the recovery of a case of gonorrheal endocarditis treated by hyperpyrexia at the First International Conference on Fever Therapy in March 1937. Williams¹ reports a case of proved and one of probable gonorrheal endocarditis treated with artificial fever in the Kettering hypertherm. In the proved case fever treatment resulted in sterilization of the blood stream and, as established at necropsy, sterilization of the endocardial vegetations. Death, Williams attributed to a co-existing syphilitic cirrhosis of the liver and uremia. In the case designated as probable gonorrheal endocarditis, fever treatment resulted in prompt recovery. Krusen and Elkins^{1a} have also reported a case of gonococcemia with endocarditis treated with fever therapy without effect.

While Wagner-Jauregg originated true fever therapy in 1918 for dementia paralytica, it was not until the work of Carpenter, Boak, Mucci and Warren² in 1933, that fever therapy for gonorrheal infections was placed on a rational basis. These workers investigated the thermal death time of 15 strains of gonococci at 39°, 40°, 41°, 41.5° and 42° C in vitro. Seven of these strains were isolated in 1920, one in 1922 and the remaining seven were isolated one to four months previously. In all instances the "recently" isolated strains, with the exception of one "old" strain, showed the least resistance to 41°, 41.5° and 42° C. At 41.5° C and 42° C 99 per cent of the organisms were rendered non viable in two hours. At 41.5° C from seven to twenty hours and at 42° C five to fifteen hours were required for sterilization. They felt that the in vitro thermal death time was short enough at these temperatures to suggest fever therapy as a valuable therapeutic aid. They thought that complete sterilization could not be obtained with only one session of fever of five hours. Their work suggested that in vivo something other than the mere heating occurred to make the organisms

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more susceptible to destruction by the body. In 1936 Thompson, Sheard and Larson³ tested a number of organisms at 107° F. for as long as 24 hours to determine the effect at temperatures which the human body could stand. Of the organisms tested only the gonococcus showed complete sterilization, and this was true with as short a period as six hours.

Desjardins, Stuhler and Popp⁴ reported a series of 76 cases of gonorrheal infection, 36 with urethritis and 40 with complications, treated by fever therapy. They reported 89.5 per cent cured, and 9.2 per cent improved. The average number of sessions was six periods of six to eight hours per patient. They point out that advanced age with cardiovascular changes and organic heart disease at any age are severe handicaps to fever therapy. Functional heart disease may or may not interfere with satisfactory treatment. They feel that severe disturbance of renal function may make fever therapy difficult or contraindicated but will interfere less than cardiac or cardiovascular lesions. Diabetes under satisfactory control is no contraindication to treatment. Pulmonary tuberculosis itself is not a contra-indication, but the impairment of respiratory function may make it impossible to maintain safely a satisfactory temperature level. They report an increasing pulse rate at the beginning of the treatment through the phase of rising temperature and then stabilization at 120 or, more especially in unstable patients, 140 to 150 with large amplitude of oscillations. If the pulse exceeds 160, the fever is terminated at once and a new trial made two or three days later. If the pulse again rises too high, attempts at fever therapy are discontinued. They observed an almost constant rise of the blood pressure more rapidly than that of the temperature. After the maximum temperature has been reached, the systolic pressure slowly falls so that by the end of the session it is below the original level. The diastolic pressure falls slowly, 10 to 35 mm. The most important point is the careful observation of the pulse pressure, and if it is reduced to 20 mm. or less, the session should be terminated at once.

The use of fever therapy in endocarditis is not a new therapeutic procedure. Fulton and Levine⁵ report two cases of subacute bacterial endocarditis treated with rat-bite fever, another in which malarial inoculation was employed though no chills and fever resulted, a Bier operation was performed on another, two cases were given typhoid vaccine intravenously, in one of which a temporary disappearance of the fever occurred, four patients were given subcutaneous injections of turpentine to produce sterile abscesses. In one of these cases the temperature fell to normal and remained so for more than a month. None of these procedures, however, were of permanent benefit in any case.

Thayer^{6, 7} pointed out that gonorrhea is an infection, focal at first, which spreads both by local extension and by the blood stream. A general septicemia then develops with a variety of metastases, i.e., arthritis, synovitis, myositis, and not infrequently endo-, myo- or peri-carditis. He reported 23 cases of gonorrheal endocarditis, 11.6 per cent of the cases of acute endo-

carditis at the Johns Hopkins Hospital Sixteen of his cases were males and 11 of the total cases were white The age varied from 9 to 42 years Evidence of preexisting valve damage was present in only 5 of the 23 cases thus proving the observations of many clinicians of the frequency of involvement of previously undamaged valves Most cases followed urethritis Four cases followed puerperal complications The time of onset of the septicemia varied In one case the onset was almost coincident with the urethritis, in four cases within two weeks, two within a month and the remainder of uncertain time

In seven of his cases a history of arthritis in the course of the illness was obtained Thayer felt this was an unusually low incidence and in 54 cases he collected from the literature 68.5 per cent had arthritis

The symptoms are those of a septicemia The onset sometimes is gradual with headache, lassitude, sweating, vague muscle pains, or more sudden with a sharp chill as occurred in our case The majority of cases have chills and severe sweats Hamman and Wainwright⁸ point out in a study of the diagnosis of obscure fever that these symptoms are those of the classical form but that the disease may cause a relatively benign, long continued infection with a low fever, slight or absent leukocytosis and with involvement by preference of the aortic valves The diagnosis is often overlooked since the gonococcus is difficult to culture Hamman and Wainwright⁸ report 90 cases of obscure fever of which two cases were gonorrheal endocarditis and one of these was diagnosed only at autopsy Emboli are common Jaundice has been reported in patients with gonorrheal infections Popper and Weidman⁹ have written an interesting report on "Gonotoxic icterus" They believe that hepatic impairment results from gonotoxins and a picture simulating catarrhal jaundice is produced Petechiae or other skin eruptions are frequent Bakst, Foley and Lamb¹⁰ report a case of gonococcemia with erythema nodosum and have collected 18 cases from the literature with skin manifestations These skin lesions were maculopapular, pustular, macular, purpuric and urticarial The spleen was palpable in 21 per cent of Thayer's cases Clubbing of the fingers was noted in none of Thayer's cases The blood shows a rapidly developing anemia and a high leukocytosis, over 30,000 in 42 per cent of Thayer's cases The gonorrheal complement fixation is positive in a high percentage of cases and is of considerable assistance in diagnosis Blood culture showed gonococci in 10 of Thayer's cases before death and in 13 of his cases gonococci were isolated from the heart's blood or the vegetations at autopsy In one case the organism was isolated from the kidney The difficulty in obtaining a positive blood culture is one of the characteristics of this disease

Dieulafoy¹¹ reported a case in which both gonococci and pneumococci were found in the sputum Two of Thayer's cases had pleurisy and in one of these the gonococcus was cultured from the fibrinopurulent fluid The urine examination showed albuminuria, casts, leukocytes, epithelial cells and erythrocytes These signs are more marked in cases of long duration The

majority of Thayer's cases had acute or subacute nephritis, four showing anasarca and hydrops.

Thayer's study of the pathology of these cases shows the frequency of involvement of the aortic valve and the relative frequency of pulmonic valve involvement. In his series the aortic valve was involved in 66 per cent, mitral valve 19 per cent, pulmonic valve 23.8 per cent, and tricuspid valve in 23.8 per cent. The process is notably ulcerative and with exuberant vegetations, pink or gray, irregularly lobulated, soft and friable. Mitral endocarditis was present in 61.9 per cent of his cases and especially notable was involvement of the aorta. In two cases mitral involvement of the aorta was the only lesion. Pericarditis was present in 28.5 per cent of the cases.

The prognosis of gonorrheal endocarditis is not necessarily fatal. Solomon, Huitwitz, Woodall and Lamb¹² found 148 cases of gonorrheal endocarditis reported in the literature of which 10 survived despite the presence of cardiac involvement, a mortality rate of 93 per cent. A review of the literature by Bakst, Foley and Lamb¹⁰ revealed 27 cases of gonococcemia without demonstrable endocarditis with recovery.

The treatment of this condition is discouraging. *Gonococcus* vaccine has been given by many, and some of the recovered cases received vaccine. However, one of the cases reported here received vaccine with no benefit. Perry^{13,14} reports a case of unquestioned gonorrheal endocarditis treated by frequent small blood transfusions with recovery. Vaccines were tried in his case, but the reactions were so severe that this form of treatment had to be discontinued. Wheeler and Cornell¹⁵ report a case with intermittent bacteremia from a pelvic focus treated by radical extirpation with recovery. Garlock¹⁶ reports a case with a positive blood culture, diagnosed gonorrheal endocarditis, in which he performed a salpingohysterectomy. The temperature fell to normal, blood culture became negative, and the patient was discharged after seven weeks. Six months later there was no demonstrable lesion in the heart. Newman¹⁷ reports a case with recovery in which the critical drop in temperature occurred following a febrile episode during which the temperature was the highest that it had been at any time during the illness. Newman commented on this fact as of some importance in the ultimate recovery. However, other cases reported have had temperatures as high or higher without so favorable an outcome.

Dees and Colston¹⁸ report on the use of sulphanilamide in gonococcal infections. This suggests the use of this drug in the endocardial form of this disease. We hope there will be reports in the literature bearing on this phase in the near future.

CASE REPORTS

Case 1. A 48-year-old Jewish business man was first seen June 30, 1936 complaining of chills, fever and severe sweating of one week duration. On April 13, 1936 he had had an acute gonorrheal urethritis treated by local injections. On June 8, 1936 he had a left epididymitis treated by bed rest and applications of ice. On

June 21 he had a chill followed by a feeling of fever and sweating. The following day he noted a punctate skin rash on the left leg, hands and left arm.

The patient's family and social histories were essentially irrelevant except for sexual irregularities. The past history was irrelevant except for gonorrhea in 1927. Physical examination at his home on June 30 revealed a well developed and nourished white male not appearing acutely ill. The head and neck were entirely normal. There was no cervical, axillary or inguinal adenopathy. The thorax was symmetrical and expanded equally and well. The apex impulse was visible 8 cm from the mid-sternal line in the fifth interspace, the right heart border was at the right sternal margin. No palpable thrills were felt. Heart tones were normal and no murmurs were heard. A_2 was greater than P_2 . Blood pressure was recorded at 120 mm of Hg systolic and 75 mm diastolic. The radial pulses were equal and regular at a rate of 88.

The lung fields were normal to percussion and auscultation. Examination of the abdomen was normal. The liver, spleen and kidneys were not palpable. Examination of the genitalia revealed a small amount of clear mucous discharge from the urethra which did not show gram negative intracellular diplococci. The right testicle was not completely descended and was palpable just above the pubis. The left testicle was somewhat enlarged, and the epididymis was nodular, thickened and moderately tender. Rectal examination revealed a somewhat nodular, non-tender prostate of normal size. On the left lower leg, both hands, and on the left arm were 15 or 20 dull red lesions 2 to 3 mm in diameter. They were considered questionable petechiae. The deep tendon reflexes were equal and active in both upper and lower extremities.

Urine examination showed a specific gravity of 1.013, acid reaction, albumin, slightest possible trace, sugar negative, the sediment showed 20 to 25 white blood cells per high power field, rare finely granular casts and no red blood cells. Hemoglobin 82 per cent (Newcomber), red blood cells 4,570,000, white blood cells 14,500. Examination of a blood smear revealed no malarial parasites. Differential blood count: Polymorphonuclears 77 per cent, lymphocytes 10 per cent, monocytes 5 per cent, eosinophiles 1 per cent, band forms 5 per cent, young lymphocytes 2 per cent. Agglutination tests for typhoid, paratyphoid a and b and undulant fever were negative. Complement fixation for gonorrhea was positive.

During the following week the patient's temperature was as high as 102° (F) on two evenings and these rises were followed by drenching sweats. Roentgen-ray examination of the chest on July 6, 1936 showed no evidence of pulmonary disease or cardiac enlargement. July 7, 1936 he was admitted to the Peter Bent Brigham Hospital with a diagnosis of suspected gonorrheal bacteremia. The history and physical examination were essentially as given above. Urine examinations showed a specific gravity from 1.005 to 1.007, no albumin or sugar. The sediment showed 25 to 50 white blood cells on one occasion and 3 to 5 thereafter. Hemoglobin 95 per cent (Sahli), red blood cells 4,680,000, white blood cells 9,500. Differential blood count essentially as before. Blood Hinton negative. Phenolsulphonephthalein test showed 40 per cent excretion in two hours and 10 minutes.

A blood culture taken July 8, 1936 showed a gram negative diplococcus. The blood was drawn into dextrose broth and cultured under partially anaerobic conditions for four days. Transfers were then made to a chocolate agar slant and a few small colonies grew out under partial anaerobiosis, but no growth occurred under aerobic conditions. On blood agar slants there was moderate growth under partial anaerobiosis after several days but no growth under either completely aerobic or anaerobic conditions. There was no acid or gas formation in cultures with dextrose, maltose, lactose, xylose or mannite even after the addition of fresh normal blood. In dextrose broth under aerobic conditions at 37° C there were a few gram negative diplococci on a loop smear after 10 days. Anaerobically at 37° C there was no growth in

dextrose broth nor was there growth under any condition at room temperature. In an approximate 1:2 dilution with antimeningococcic serum there was no agglutination. Culture taken on July 9 showed a similar organism but a culture taken on July 13 showed no growth after eight days. During the week in the hospital his temperature ranged from 101.8° F to 97° F. The pulse ranged from 98 to 68. Respirations averaged 20 per minute. At the patient's request he was discharged to his home, July 14, 1936. At no time during the hospital stay was there any change in the physical findings. The heart showed no murmurs. The blood pressure was consistently 110 to 120 mm Hg systolic and 75 to 80 mm Hg diastolic.

During the following week he continued to have a daily rise in temperature with several severe chills. A soft basal systolic murmur was heard July 19. He was advised to return to the hospital for fever therapy.

He was readmitted to the Peter Bent Brigham Hospital July 21, 1936 and received his first treatment July 22, 1936. Fever therapy was given with diathermy, the temperature being elevated to 105.6° to 106.6° F (rectal) for three hours. During the treatment the pulse varied from 132 to 138 and was of good quality.

On July 24 (103 days after the onset) a blowing diastolic murmur was heard along the left sternal border loudest in the third interspace. The blood pressure was 108 mm Hg systolic and 60 mm Hg diastolic. There did not appear to be any change in symptoms though he had complained of some sense of pressure over his chest after the first treatment.

July 24. Second fever therapy treatment. The temperature was raised to 106.2° F (rectal) in the diathermy machine and prolonged 3½ hours. The patient's pulse varied from 134 to 140 during the treatment. After the treatment he appeared to be in relatively good condition. July 25, blood pressure 108 mm Hg systolic and 52 mm Hg diastolic. The diastolic murmur was louder than before. There was also a soft apical systolic murmur. The blood pressure was 108 mm Hg systolic and 52 mm Hg diastolic.

July 27. Third fever therapy treatment. Temperature maintained at 106° F (rectal) for two hours 10 minutes. Patient then complained of feeling weak and the treatment was stopped. July 28. There was a loud blowing diastolic murmur now audible at the base and along the left sternal border. The systolic murmur had also become more harsh and loud. Blood pressure was 110 mm Hg systolic and 58 mm Hg diastolic. The lung fields were clear to percussion and auscultation. The liver edge was palpable 2 cm below the right costal margin and moderately tender. The spleen was not palpable. The left epididymis was somewhat more tender than before. The prostate was not enlarged or tender. There was no peripheral edema and no petechiae or clubbing of the fingers.

July 20. Fourth fever therapy treatment. Rectal temperature maintained at 106° to 106.4° F for 4½ hours. Pulse 116 to 124 during treatment. Blood pressure 108 mm Hg systolic and 48 mm diastolic.

July 31. Hemoglobin 76 per cent, red blood cells 4,160,000, white blood cells 13,000. Differential count: Polymorphonuclears 90 per cent, lymphocytes 5 per cent, eosinophiles 2 per cent, monocytes 3 per cent.

August 2. Fifth fever therapy treatment. Temperature raised to 106° to 106.4° F for 4½ hours. August 6. The patient was obviously failing. Transfusion of 400 cc of citrated blood was followed by a severe reaction. Both the diastolic and systolic murmurs became much louder. The liver was palpable 2 cm below the right costal margin. The respirations were 40 to 50 and the pulse 100 to 120. He had frequent attacks of weakness with increased dyspnea. He gradually became weaker and died August 13.

Clinical Diagnosis. Gonococcal sepsis, gonorrheal endocarditis with involvement of the aortic valve. Left epididymitis. Bilateral hydrothorax. Pulmonary edema.

Postmortem Examination No free fluid in the peritoneal cavity The liver extended 4 cm below the right costal margin The spleen was markedly enlarged with a few adhesions over the surface On section there were areas of infarction

The right pleural cavity contained 450 cc and the left 750 cc of cloudy fluid The pericardial cavity contained 60 cc of straw-colored fluid and showed smooth moist surfaces

The heart weighed 470 grams before fixation and 395 grams after fixation Valve measurements Tricuspid valve 10 cm, pulmonary valve 6 cm, aortic valve 6.5 cm, mitral valve 8 cm The aortic valve was the site of an acute ulcerative endocarditis The left posterior cusp of the aortic valve was nearly split into two portions by a granular, productive lesion which rose slightly above the normal height of the free edge of the leaflet The lesion also penetrated the wall of the adjacent anterior cusp extending directly through it in continuity at the attachment of the cusp It then produced a rather flat papillomatous projection on the inner aspect of the lateral margin of the anterior cusp (Figure 1) The free margin of the anterior cusp was freely moveable, translucent but fixed by the penetrating growth at the junction with the left posterior cusp The right posterior cusp was free from involvement The openings to the coronary vessels were not encroached upon by the lesion There was slight bulging of the *annulus fibrosus* of the pulmonary valves from the ulcerative action of the lesion in penetrating from the left posterior to the anterior cusp of the aortic valve The tricuspid, pulmonary and mitral valves were not involved in the ulcerative process The myocardium was of a uniform reddish brown color and free from evidence of infarction The papillary muscles and chordae tendineae of both mitral and tricuspid valves appeared normal

Microscopic sections showed Aschoff bodies in the myocardium Sections from the vegetations on the aortic valve showed a mass of necrotic debris surrounded at its base by a few polymorphonuclear leukocytes There were some colonies of bacteria in the necrotic material and some scattered bacteria were also seen In the eosin-methylene blue and Giemsa stained sections were found small biscuit shaped diplococci, many of which were intracellular These were decolorized in the sections stained by Gram's method and hence were gram negative

The lungs showed a diffuse bronchopneumonia

The gastrointestinal tract and pancreas were essentially normal The right kidney showed old infarcts—the left kidney was markedly enlarged and showed multiple metastatic abscesses The bladder showed congestion and ecchymosis at the bladder neck and there was inflammation throughout the prostatic urethra The prostate was of normal size, but showed multiple abscesses with numerous biscuit shaped diplococci on microscopic section The epididymis showed diffuse inflammation The seminal vesicles showed swelling and edema, but no abscesses The left testicle showed purulent fluid in the tunica vaginalis which showed gram negative organisms on smear, not definitely diplococci

Postmortem Diagnosis Acute aortic endocarditis, gonococcal, rheumatic myocarditis, bronchopneumonia, empyema, bilateral, acute and chronic epididymitis, acute urethritis, acute pyelonephritis, multiple abscesses of left kidney, infarction of right kidney, acute splenitis, chronic cystitis, acute and chronic prostatitis and vesiculitis, hydrocele, left, infected, basophilic infiltration of posterior lobe of pituitary

Case 2 A white, married female, aged 28, was admitted August 9, 1922, complaining of chills and fever of three and one half months' duration She had had a thick yellow vaginal discharge for 18 months following a questionable spontaneous abortion From the family physician it was learned that there was a definite history of gonorrheal infection preceding the present illness Her husband had been treated for gonorrheal urethritis at the Boston Dispensary on several occasions In April 1922 she had an upper respiratory infection and at that time had some dysuria and



FIG 1 Arrow I points toward vegetations on ruptured left posterior valve cusp of aortic valve. Arrow II points to vegetation at base of anterior valve cusp.

urgency Following this there was an increase in the vaginal secretion which persisted until admission Since April she had noticed an increasing weakness and since May she had had night sweats and severe chills almost nightly The family history and past history were irrelevant Inventory by systems revealed no additional data

Physical examination showed a fairly well developed somewhat wasted woman The face was pale and thin On the bottom of the left great toe was a petechial hemorrhage Examination of the head and neck yielded no relevant findings The thorax was symmetrical and expanded equally and well Examination of the heart as reported by Dr Samuel A Levine on August 12, 1922 showed a systolic thrill at the apex and a questionable short thrill in diastole The apex impulse was seen and felt 11.5 cm from the midline Left border of cardiac dullness was 12.5 cm from the mid sternal line, the right border of dullness was not made out No increased submanubrial dullness was made out The heart sounds were regular and rapid The first sound at the apex was slightly booming followed by a systolic murmur and an early long diastolic murmur On approaching the base a different harsher systolic murmur was heard and a typical aortic diastolic murmur along the left sternal border The radial pulses were equal, regular and synchronous The blood pressure was 128 mm Hg systolic and 54 mm diastolic The lungs were clear to percussion and auscultation Palpation of the abdomen revealed that the spleen was easily felt two fingers below the left costal margin The liver and kidneys were not palpable There was moderate clubbing of the fingers A cervical smear showed no gram negative intracellular diplococci Pelvic examination showed no evidence of pelvic inflammatory disease

Examination of the blood showed 80 per cent hemoglobin, 3,850,000 erythrocytes, 12,200 leukocytes A differential leukocyte count gave 83 per cent polymorphonuclears, 12 per cent lymphocytes, and 5 per cent monocytes Anemia developed rapidly and on October 10 the hemoglobin was 35 per cent and the erythrocytes 1,955,000 Urine examination Acid reaction, specific gravity average 1.008, albumin varying from slight trace to large trace, sugar negative, the sediment showed many leukocytes and erythrocytes, and many cellular and brown granular casts

Blood Wassermann negative Complement fixation for gonorrhea negative Five blood cultures showed no growth Electrocardiograms showed left axis deviation

The temperature curve was of the picket fence type, the fever reaching 105.8° F and varying between 98° F and that level The blood pressure gradually fell and on October 9 was 86 mm of Hg systolic and 38 mm diastolic Transfusion of 300 c.c. of blood from the patient's husband was followed by a severe reaction with temperature rise to 106° F Sodium cacodylate was given intramuscularly, 0.05 gm, twice daily without altering the course of the disease The patient died October 18, 1922

Postmortem examination revealed 1400 c.c. of clear yellowish fluid in the peritoneal cavity with the spleen enlarged and showing two infarcts The liver extended 4 to 5 cm below the right costal margin The pleural cavities contained no free fluid The lungs showed a definite pneumonia The kidneys showed cortices thicker than normal and microscopically some of the glomeruli showed adhesions to the capsule and in several thrombi were present The pericardial cavity contained 210 c.c. of bloody fluid with flecks of fibrin The parietal pericardium was thickened and covered with a yellowish film of fibrin in places thrown into ridges and folds Smears from the fibrin showed gram negative diplococci and a few polymorphonuclear cells Cultures from heart blood yielded a gram negative and gram positive bacillus thought to be terminal invaders as no such organisms were isolated elsewhere

The heart weight was estimated at 450 grams The epicardium was covered with yellowish soft exudate thrown up into folds giving a shaggy appearance The

tricuspid, mitral and pulmonary valves were normal. The aortic valves were somewhat thickened and attached along the margins of the cusps were soft, pinkish vegetations measuring up to 4 to 5 mm in diameter. Smears from the vegetations revealed a gram negative diplococcus. On blood agar a growth of *Staphylococcus aureus* and diphtheroid bacilli were produced from the vegetations. The entire arch of the aorta seemed dilated. In addition there were several aneurysms with sharply outlined orifices present. There were two aneurysms about 0.5 cm by 1.0 cm just above the valve, tending to extend out from the right side of the aortic arch and to bulge into the epicardium. These aneurysms were filled with reddish, granular thrombi. There was a large, sharply delimited aneurysm 2.5 cm in diameter extending from the bottom of the arch of the aorta. Smears of the friable globular masses of clot in this aneurysm revealed masses of gram negative diplococci, apparently in colony form. A few polymorphonuclear cells were filled with gram negative diplococci. The morphology of these organisms was consistent with that of the gonococcus.

The postmortem diagnosis was acute aortic endocarditis, gonococcal, mycotic aneurysm of arch of aorta (gonococcal), organizing fibrinous pericarditis, hypertrophy and dilatation of the heart, bronchopneumonia, infarct of spleen, ascites and chronic pleuritis.

Case 3 A 24-year-old white male was admitted December 3, 1914 complaining of weakness and fever. Three months before he had had pain, tenderness and limitation of motion in the right shoulder. Two weeks later both knees became painful and stiff. Two months before, he first noticed a daily fever and severe night sweats. There had been a weight loss of 18 pounds. The patient denied gonorrhea or syphilis. The past history revealed pneumonia and pleurisy at 10 years of age.

Physical examination revealed a well nourished white male lying quietly in bed. Examination of the head and neck was negative. The left border of cardiac dullness was 13 cm from the mid sternal line in the fifth interspace, the right border of cardiac dullness was at the right sternal margin. The heart sounds were regular and rapid. There was a systolic thrill at the apex and a rough blowing systolic murmur was heard at the apex and transmitted to the axilla and to the angle of the left scapula. The mitral second sound was clear. The lungs were clear to percussion and auscultation. The examination of the abdomen showed nothing of note. The liver, kidneys and spleen were not palpable. Blood pressure readings showed 100 mm Hg systolic and 70 diastolic. The patient was seen by Dr. Henry A. Christian who confirmed the heart findings and made a diagnosis of acute endocarditis. On admission, the hemoglobin was 79 per cent, white blood cells 8,400. Blood Wassermann test positive, two plus. Electrocardiograms were normal on several occasions. Phenolsulphonephthalein test showed 42 per cent excretion of the dye in two hours. On January 4 two petechiae were noted in the right conjunctiva. The patient gradually developed a severe anemia. During the first 11 days the temperature was rarely over 100.4° F, but thereafter it became "picket fence" in type rising as high as 104° F and being almost continuously above normal. The pulse varied between 90 and 130. On January 19, 1915 a faint diastolic murmur was first heard in the fourth interspace just to the left of the sternum. February 3 a pleural friction rub was heard in the left axilla and back.

He was given antigonococcus vaccine both intravenously and intramuscularly but later developed severe reactions from the vaccine so that it had to be stopped. On February 23 he complained of pain in the left chest and coughed up bright red sputum. He failed rapidly and died in several hours. No postmortem examination was done.

Blood cultures taken on December 4, and December 12, 1914 showed a small short chained coccus growing 3 to 5 cm below the surface in the dry tube dextrose ascitic agar. No growth was obtained on the plates. Blood culture taken on January 4, 1915 on dextrose ascitic agar plates and tubes showed, after 64 hours in-

cubation, numerous, minute grayish white colonies. Smears showed a small gram negative coccus occurring in pairs and small groups. On subculture growth was obtained on dextrose ascitic agar and in plain ascitic bouillon. On agar slants growth appeared in 48 to 64 hours as fine dew drop colonies. The notation was made "the organism has all the characteristics of gonococcus."

Clinical diagnosis Acute endocarditis, gonococcal

DISCUSSION

These cases illustrate the destructive nature of the lesions of gonococcal endocarditis. In the first case one cusp of the aortic valve was practically destroyed. In the second case there were multiple aortic aneurysms in association with an aortic endocarditis with small vegetations.

The difficulty in culturing gonococci from the blood stream is illustrated by the second and third cases. In the second case it was not possible to culture the organism before or after death. The diagnosis in the second case is based on the typical pathology, the appearance and the staining reactions of the organism as seen in the lesions and the history. In the third case there was difficulty in identifying the organism. In the first case cultures were satisfactorily obtained only under partial anaerobiosis.

It is most important to differentiate definitely the organism isolated from the meningococcus because of the difference in therapy and prognosis. Meningococcus endocarditis while rare does occur. Rhoads¹⁹ reported a case of endocarditis due to the meningococcus in 1927 and collected 11 case reports in the literature. In several of these cases no signs of meningitis were observed. One case showed swelling of the joints of the ankles and fingers. Necropsy showed adhesive pericarditis and a cauliflower vegetation on the mitral valve. Several of the cases showed only a vegetative endocarditis but Rhoads' case was marked by its ulcerative character. The vegetative process had ulcerated through the interventricular septum and involved the medial cusp of the tricuspid valve and also the base of the aortic valve. Ross and Greaves²⁰ report a case of probable meningococcus endocarditis which reacted to specific serum therapy and recovered though with severe cardiac damage.

In our first case the presence of a rheumatic myocarditis was not suspected. There was no past history to suggest such a condition, except for the illness of the previous year when a cholecystitis or coronary occlusion was suspected. Neither of these conditions was diagnosed, as the electrocardiograms and roentgenological studies were normal. There was no gross or microscopic evidence of previous valve damage apparent, which bears out Thayer's conclusion that gonococcal endocarditis is more frequent on undamaged valves.

After studying the various methods in use up to that time (June 1936) in treating gonococcal endocarditis we felt that fever therapy offered a more rational method of treatment than any which had been tried. Careful work had shown that the gonococcus is susceptible to temperatures the human

body can stand. The first patient had a total of seventeen and one-half hours of fever therapy in five sessions, with temperatures of 105.6° to 106.6° F (rectal) in the first three hour session and 106° to 106.4° (rectal) thereafter. We felt this should have been enough to produce the desired result. However, we did not determine the thermal death time of the particular gonococcus isolated in this case and therefore we cannot state definitely that the amount of fever therapy was sufficient from a theoretical point of view. In future cases this should be done. We do not feel that fever therapy increased the rate of progress of the disease nor did it slow the process.

SUMMARY

1 Three cases of gonorrheal endocarditis are reported. The diagnosis in the first case was made clinically and was proved at autopsy. The organisms were isolated from the blood stream during life and were present in sections from the affected valves at autopsy. The diagnosis in the second case was made clinically. The organism was not isolated from the blood stream during life, but smears from the vegetations at autopsy showed gram negative diplococci and the gross pathology was typical of gonorrheal infection. The diagnosis in the third case was based on the clinical course and history and the isolation of the gonococcus from the blood stream during life.

2 The first case was treated with fever by means of diathermy. A total of seventeen and one-half hours treatment was given at 106° F (rectal). The second case was treated by general supportive measures. The third case was treated with antigonococcus serum. All three were fatal.

We wish to thank Dr Israel Kopp for his cooperation in treating this patient with fever therapy at the Boston Psychopathic Hospital.

BIBLIOGRAPHY

- 1 WILLIAMS, R. H. Gonococcal endocarditis treated with artificial fever (Kettering hypertherm), *Ann Int Med*, 1937, 2, 1766.
- 1a KRUSEN, F. H., and ELKINS, E. C. Fever therapy for gonococcemia and meningococcemia with associated endocarditis: report of two cases, *Proc Staff Meet Mayo Clin*, 1937, 12, 324.
- 2 CARPENTER, C. M., BOAK, R. A., MUCCI, L. A., and WARREN, S. L. Studies on the physiological effects of fever temperatures, *Jr Lab and Clin Med*, 1933, xviii, 981.
- 3 THOMPSON, L., SHEARD, C., and LARSON, N. The effect of heat at 107° F (41.8° C) on various bacteria, *Proc Staff Meet Mayo Clin*, 1936, 11, 319.
- 4 DESJARDINS, A. U., STUHLER, L. G., and POPP, W. C. Fever therapy for gonococcal infections. XII, *Jr Am Med Assoc*, 1936, cvi, 690.
- 5 FULTON, M. N., and LEVINE, S. A. Subacute bacterial endocarditis with special reference to the valvular lesions and previous history, *Am Jr Med Sci*, 1932, clxxxiii, 60.
- 6 THAYER, W. S. On the cardiac complications of gonorrhea, *Bull Johns Hopkins Hosp*, 1922, xxxiii, 36.
- 7 THAYER, W. S. Studies on bacterial (infective) endocarditis, *Johns Hopkins Hospital Rep*, 1926, xlii, 1.

- 8 HAMMAN, L, and WAINWRIGHT, C W The diagnosis of obscure fever II Diagnosis of unexplained high fever, Bull Johns Hopkins Hosp, 1936, lviii, 307
- 9 POPPER, H, and WEFIDMAN, A Ueber gonotoxischen Ikterus, Ztschr f klin Med, 1937, cxxxii, 258
- 10 BAKST, H J, FOLEY, J A, and LAMB, M E Gonorrheal septicemia and erythema nodosum, ANN INT MED, 1935, ix, 790
- 11 DIEULAFOY, G Gonococcic septicemia, Internat Clin, 1909, iii, 59
- 12 SOLOMON, P, HURWITZ, D, WOODAIL, M, and LAMB, M E Diagnosis of gonococcus endocarditis, Arch Int Med, 1933, lxi, 1
- 13 PERRY, M W Gonorrheal endocarditis with recovery, a case report, Am J Med Sci 1930, lxxix, 599
- 14 PERRY, M W Further note on a case of gonorrheal endocarditis with recovery, Am J Med Sci, 1933, lxxxv, 394
- 15 WHEELER, G W, and CORNELL, N W Gonococcal bacteremia in a woman with apparent cure by surgical intervention, Jr Am Med Assoc, 1930, xciv, 1568
- 16 GARLOCK, J H Gonococcal bacteremia in a woman with cure by surgical intervention, Jr Am Med Assoc, 1931, xcvi, 999
- 17 NEWMAN, ALBERT Prognosis in gonococcal endocarditis, Am Heart Jr, 1933, viii, 821
- 18 DEES, J E, and COLSTON, J A C Sulfanilamide in gonococcic infections, Jr Am Med Assoc, 1937, cxviii, 1855
- 19 RHOADS, C P Meningococcus endocarditis, Am J Path, 1927, iii, 623-629
- 20 ROSS, C W, and GREAVES, F C Gonococcic and meningococcic endocarditis, with report of three cases, U S Nav Med Bull, 1935, xxxiii, 179-183

BUCKLING OF THE RIGHT COMMON CAROTID ARTERY IN HYPERTENSION

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IN 1925, Brown and Rowntree described a characteristic buckling of the right common carotid artery which is present in some severe cases of hypertension. A review of the literature^{1,2,5} revealed that such limited recognition has so far been accorded this sign that it seemed opportune to call attention to its frequent occurrence in cases of hypertension and to the mistakes in diagnosis often caused by its non-recognition. We are also reporting two new cases in which buckling of the right common carotid artery occurred. These cases were observed in a study of 48 consecutive hospital cases of white patients who had essential hypertension.

Buckling in such cases consists in a kinking or angulation of the right common carotid artery out under the skin, which buckling is prominent enough to result in a pulsatile mass. This condition must not be confused, however, as has already been done by one writer,² with other and far more frequent pulsations in the region of the neck which are seen both in health and disease. What distinguishes buckling from them is the tumor-like deformity which is visible behind the lower third of the sternocleidomastoid muscle. The location of the buckling of the carotid artery as well as its general characteristics often cause it to be confused with carotid and subclavian aneurysm. It should likewise be kept in mind when considering suspected instances of hyperthyroidism.

In all the cases of hypertension with buckling of the carotid artery so far reported the patients have been nonsyphilitic and the buckling has been in the lower anterior part of the neck just above the right sternoclavicular joint. Buckling has never been seen on the left side. Brown and Rowntree's patients were all white women. Beardwood's two patients were negroes, one of them a male. It does not appear, therefore, that the condition is limited to any one race, but we expect that it has a predilection for the female sex. Beardwood's cases are of further interest because, in both of them, the patients were able to state definitely that as far as they knew the pulsating mass was of recent origin.

Brown and Rowntree thought that kinking of the common carotid artery was "the mechanical sequence of the arch elevation, although elongation through increased intra-vascular pressure also contributes to its tortuosity." Figure 1 shows the relative change brought about in this way. It is of interest to note that surgeons operating on tonsils have often reported tortuosity in the internal carotid arteries, and have speculated about the possibility that this tortuosity may represent a reversion to a lower phylogenetic type.

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These views have been based on the belief that, in seals, the carotid arteries were much longer than the distance they transversed and consequently were not straight. Recently, a very careful study⁴ was made of this problem, and it appears that neither in seals nor in any other form of animal life has anybody ever demonstrated a normal tortuosity in either carotid vessel. The theory of reversion to a lower type therefore has no basis. Besides, so far as we know, buckling of the carotid artery has never been reported in patients without hypertension. It would seem, therefore, that the explanation of Brown and Rowntree best elucidates the mechanism of its formation.

In making the diagnosis of buckling one must remember that the condition occurs in cases of hypertension, mostly in women, and apparently only in the right side of the neck. One should attempt to demonstrate elevation

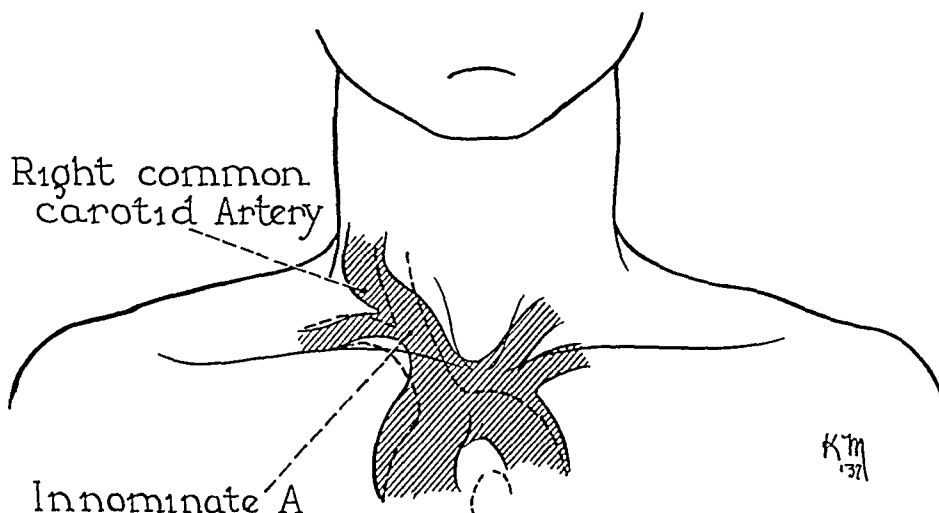


FIG 1 Buckling of right common carotid artery in hypertension. Increased blood pressure raises the aortic notch, and perhaps elongates the individual arteries. Consequently, the right common carotid artery is pushed outward and upward. The relative position before and after this change is here illustrated. Notice the beginning point of buckling on the heavily shaded carotid artery.

of the aortic arch, either by palpating the episternal notch or by studying a roentgenogram of the thorax. Most important in the diagnosis is actual palpation of the carotid artery itself. In this way one can show the point of angulation, and often establish that the diameter of the vessel has not changed. The pulsation in a buckled artery does not have the expansile quality present in aneurysm. Those who make it a practice⁶ routinely to palpate the carotid arteries in cases of suspected cerebral arteriosclerosis have not yet reported the occurrence of buckling in patients with arteriosclerosis but without hypertension. Buckling tends to diminish in prominence when the blood pressure lowers.¹

CASE REPORTS

Case 1 A Spanish woman, 47 years old, who had had hypertension for the previous four years, registered at the clinic on July 26, 1937. For the previous

nine or ten months she had noticed a pulsating mass in the right lower part of her neck. On admission the blood pressure in millimeters of mercury was found to be 210 systolic and 146 diastolic. When taken at hourly intervals over a period of 24 hours there was a systolic range of blood pressure from 140 to 210 mm, and a diastolic range of 90 to 140 mm, the mean systolic pressure was 190 and the mean diastolic pressure 115. Examination of the ocular fundi revealed moderate sclerosis and narrowing of the retinal arteries, slight retinitis, but no edema of the optic disks. General physical examination, except for the buckling of the right common carotid artery (figure 2), gave essentially negative results. Urinalysis showed albumin, grade 1, but no erythrocytes, pus or casts. The blood count was normal. Flocculation tests for syphilis by the Kline, Hinton and Kahn techniques were negative. A roentgenogram of the thorax and the electrocardiogram gave no additional information. The value for blood urea was 20 mg per 100 c c.



FIG 2 Buckling of right common carotid artery in hypertension. Showing the relation of the visible bulging to the tortuosity palpated in the underlying vessel.

Surgical treatment was undertaken for the relief of the hypertension. In two stages, on August 10 and September 1, Dr Adson performed extensive right and left splanchnic nerve resection. He also removed the first and second lumbar sympathetic ganglions and the celiac ganglion on each side. The postoperative course was uneventful. When the patient left the hospital it was noticed that, with the decrease in blood pressure, buckling had become less prominent. At the time of dismissal her blood pressure ranged between a maximum of 145 systolic and 90 diastolic and a minimum of 130 systolic and 80 diastolic.

Case 2 An Irish woman, 44 years old, a year previous to admission had a systolic blood pressure of 250 mm of mercury, at which time she regarded herself in good health. In the ten months preceding her admission, however, her general health had failed and she gradually complained of increasing weakness and in the last six months had lost 54 pounds (24.5 kg). When admitted to the hospital on August 2,

1937, she complained of marked dyspnea at rest, moderate orthopnea, frequent palpitations, and constant headache and throbbing at the temples. For the previous two years she had noticed a pulsating mass in the right lower portion of her neck, this mass had not changed in size, however, or given her any discomfort. On general physical examination the patient appeared to be exhausted, she was emaciated and there was cardiac enlargement, pitting edema of grade 2 of the lower extremities, the liver was palpable and buckling of the right common carotid artery was present. The artery could be palpated in remarkable detail. The blood pressure taken at hourly intervals over a period of 24 hours showed a systolic range of 220 to 250 mm and a diastolic range of 140 to 170 mm, the mean systolic reading was 230, the mean diastolic 150. Examination of the ocular fundi revealed advanced sclerosis and narrowing of the retinal arteries, marked retinitis, and some edema of the disks. A diagnosis of malignant hypertension was made. Urinalysis revealed albumin, grade 1, but no erythrocytes, pus, or casts. Hemoglobin equaled 80 per cent of normal, erythrocytes numbered 3,780,000 and leukocytes 7,100 per cu mm of blood and the differential count was normal. The Kline, Hinton, Kahn and Kolmer tests were negative. The value for blood urea was 18 mg, and for serum proteins 6.1 gm per 100 cc. An electrocardiogram showed left ventricular preponderance, normal rhythm, and some myocardial damage. The patient was dismissed from the hospital on August 5, and died at home six days later. Necropsy performed by her local physician is reported to have confirmed the diagnosis made at the clinic.

COMMENT

In case 1, the pulsating mass in the right side of the neck had been thought to be an aneurysm of the right common carotid artery. More than one physician had seen the patient and this diagnosis had been seriously considered. Careful examination, however, revealed marked buckling of the artery (figure 2). The same comment also applies to case 2. If one has in mind the possibility of buckling of the right common carotid artery, such as frequently occurs in severe cases of essential hypertension, he should have no difficulty distinguishing it from aneurysm. The differentiation of these two conditions, needless to say, is most desirable in view of the very different prognosis in each case. Aneurysm is always, by itself alone, a definite potential liability. Buckling, on the other hand, calls for no special measures, it never enters into the prognosis of the case, the prognosis in such cases depending entirely on the severity and nature of the hypertension.

REFERENCES

- 1 BEARDWOOD, J. T., JR. Right-sided carotid pulsation in hypertension, *Med Clin N Am*, 1931, *xiv*, 989-992.
- 2 BOLOTIN, M. T. Right carotid and other pulsations in essential hypertension, *Med Jr and Rec*, 1933, *ccxxvii*, 419-420.
- 3 BROWN, G. E., and ROWNTREE, L. G. Right-sided carotid pulsations in cases of severe hypertension, *Jr Am Med Assoc*, 1925, *lxxiv*, 1016-1019.
- 4 CARMEL, A. G. An inquiry into the phylogenetic basis of the flexuous *arteria carotis interna* of man (the *arteriae carotides* of the seal), *Anat Rec*, 1928, *xxix*, 343-347.
- 5 HOLST, J. E. Pulsation in right carotid artery in arterial hypertension, *Hospitalstid*, 1934, *lxxvii*, 79-84.
- 6 MONIZ, EGAS. La palpation des carotides comme element de diagnostic de l'arterio-sclerose cerebrale, *Rev Neurol*, 1930, *ii*, 48-51.

SOME DESIRABLE SUPPLEMENTS TO THE PRESENT TRENDS IN MEDICAL INVESTIGATION

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TRULY the advances in Medicine have been prodigious in the last few generations. These advances have taken place on a broad front and continually make possible the utilization not only of the so-called basic Medical Sciences but also of all branches of sciences for the understanding of disease and, indeed, often for application at the bedside.

The changing situation has developed in internal medicine new attitudes and new standards. It is not too much to say that a new specialty has appeared, that of the medical investigator. Within 50 years, to meet the needs of these medical investigators, Medical Schools and Hospitals have increased manifold and the printed product of this activity has increased many times more.

In these perhaps bewildering changes there seems at times to be a restless activity of feverish intensity. In the training and development of the internist perplexing questions arise. Granted that the internist worthy of the name should participate in medical advances and should, irrespective of age, be a medical investigator, should his work be evaluated on actual publications, on quantity of publications, and what are some of the necessary criteria for the scrutiny of the quality? Or, again, is not "furor scribendi" actually at a premium in the market of medical investigation? Or has there not developed a technic in medical investigation that is stereotype, narrow, and inadequate?

Indeed it would be surprising if, in the midst of rapid and bewildering changes, dealing with possible near or remote application of newly acquired data to that complicated mechanism called man or animal, if you will, errors and faults did not accompany the difficulties. Though the pace is fast, it should be possible to pause in order to strengthen some of the points of weakness of the present system. Obviously, careful objective observation must be the foundation of any investigation whether in Medical Science or in any other branch of science. But unless the scope of these observations is carefully planned and unless the experiments are carefully designed, the labor may be wasted. Indeed the critical observation or experiment is relatively rare. And while we may grant that trial runs are useful in familiarizing the observer with the technic and the field, we have to admit that in the large majority of instances, perhaps approximately 90 per cent, the design or plan or observation or experiment is so bad or inadequate that the entire procedure is really valueless.

If we add to this, those instances in which the statistical requirements are not met, a further wastage is apparent.

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And finally often hard reasoning is necessary to determine the conclusions to be drawn. This reasoning must satisfy the requirements of logic and must not be colored by wishful or illogical thinking.

The myth of the athletic heart is an excellent example of a product of faulty observation, of the failure to understand and use ordinary statistical principles, and of faulty reasoning throughout, especially in the conclusions based on the physiologic principle that muscular exercise increases the size of the heart, somehow erroneous observations appeared in print aiming to show the increase of the heart under athletic training, especially in colleges. A few cases of cardiac disease or death were cited to furnish the statistical evidence. Then extraordinary conclusions of all sorts were made. However, instruments of precision showed the original observations to be erroneous. But the myth was kept alive by a credence in the statistical evidence although this evidence satisfied no statistical requirement. Indeed, it is difficult to secure adequate data to meet any reasonable statistical requirements for the proof that athletic training in youth predisposes to cardiac death 20 to 40 years later. Certainly a little thought indicates many other factors that might affect the heart in addition to college athletics. Of course, any conclusions based upon such faulty observations and statistics are worthless. But highly colored conclusions were drawn. Unfortunately the myth still lives although in a feeble state.

Medical science is a young and new science. It aspires to a place alongside of the physical and natural sciences. And there are careful workers in the laboratory and in the clinic whose technic places them on a par with the scientists in other fields. In clinical medicine, Hippocrates, Jenner, Oliver Wendell Holmes, Reginald Heber Fitz, and one of the Fellows of the American College of Physicians who is on this program, James B. Herrick, are but examples of a considerable group. Relatively speaking this group is small and there is real danger that there may be a separation between this group and the other medical investigators. There ought not to be a dual standard, one good and the other debased, with the probable result that medical science will settle into the soft mud of careless methodology.

Much has always been made of the importance in medicine of observation. Every medical student is impressed by the paramount necessity of the trained use of touch, sight, hearing, smell and occasionally of taste. There are many mechanical devices to assist those senses. The use of the stethoscope is a classic example. The visual aids, which include the microscope, ophthalmoscope, cystoscope and the like, have been a large factor in modern medicine. It is indeed hard to conceive of medical science without the microscope.

But in the present onward rush of medical progress, other faculties are needed to supplement these observational senses. Hippocrates and his group were masters in the art and science of observation. We have coming down

to us, after two thousand years, many clearly defined clinical pictures as true today as then. But the conclusions of Hippocrates, while based upon accurate and repeated observations, were arrived at by careful deductions. These deductions were as carefully controlled as the observations themselves. Likewise, Jenner observed cow pox in milk maids. By the simple statistical collection (no doubt unconscious on his part) of these data, Jenner noted in a sort of statistical fashion that most milk maids contracted cow pox. His (still probably unconscious) statistical data showed that human or small pox was rare among milk maids, or, in other words, there was a high correlation between the incidence of cow pox and the absence of small pox. Jenner next (unconsciously doubtless once more) called upon another faculty or trait or whatever you care to call it of his mind, and inferred or deduced that the cow pox protected against small pox. If his observations were correct and if there were no unknown disturbing factors, this deduction was logical and it was so subsequently proved by the accumulation of abundant statistical data and the establishment of a high correlation of absence of small pox and the presence of cow pox.

In some ways, medicine has not changed in the development of the use of statistics or the use of deduction since the days of Hippocrates or of Jenner.

We have done decidedly better in regard to statistics than in regard to deductive reasoning. The simple statistics of Hippocrates and Jenner have served their purpose. The same is true of the simple correlations of Osler and Cabot. Most of us are now familiar with the punched cards of statistical technique. It took us a long time to realize that mortality figures in pneumonia had to be broken up into age groups and also into types of the infecting pneumococcus. Then, too, there may be a yearly or seasonal variation. Nevertheless, many men assert that, irrespective of statistics, certain procedures in pneumonia do good and are accompanied by a lessened mortality.

At one time, based upon electrocardiographic evidence, it was urgently advocated that digitalis be used in every case of pneumonia. Without statistical proof and without sound reasoning, the use of digitalis became, almost overnight, practically a routine procedure in the treatment of pneumonia. Subsequently, however, careful clinical studies under adequate statistical control indicated that the routine of employment of digitalis was actually detrimental to the average case. From time to time, it is the fashion to deride statistics, but the observational data which go into the statistical treatment (like the beef that goes into the can) are not changed by the process. The method is less faulty than the data. It is a long road to prove statistically the benefit of a therapeutic procedure in pneumonia. Very likely, there are still other unrecognized variables besides age groups and types of pneumonococci. Animal experiments and test tube researches are illuminating but the final answer to the query of the beneficial effect of a procedure in pneumonia in humans must be statistical.

It is certain that if data do not meet simple statistical requirements, it is quite futile to try to draw conclusions from them. In the laboratory and at the bedside, we may usually safely assume that the actual observations are accurate. It is necessary as the next step that these observations meet certain statistical requirements. Then, as a final step, deductions are made from these data.

It must be remembered that a diagnosis is rarely an observation. Pneumonia as a diagnosis is not an observation. It is a deduction.

While it is true that many of our medical errors are derived from failure to use statistics correctly, and that often means an inadequate amount of data, nevertheless, the greater bulk of our medical errors and medical difficulties are derived from faulty reasoning processes. We make many unjustifiable assumptions. We assume that we know certain facts which we actually do not know. Improper conclusions or deductions may be readily made from data which are accurate enough. For example, for many years it was argued that since malaria existed in little swamps and marshy places, therefore it was the dampness which caused the malaria.

There is one form of faulty reasoning or faulty logic which is unfortunately common in medical literature. For example, it is known that all cases of pernicious anemia have an absence of free hydrochloric acid in a gastric analysis. It does not follow, however, that all cases of absence of hydrochloric acid have pernicious anemia. Again, in pernicious anemia, most of the cases respond to liver therapy. It may be argued that liver therapy is a therapeutic test for pernicious anemia, but one must not argue that no cases are to be diagnosed as pernicious anemia if they do not respond to liver therapy and that therefore liver therapy is always successful in pernicious anemia.

Sometimes, our so-called "medical science" leads us astray as it did temporarily in the use of codliver oil in rickets. The clinical data were entirely correct as to the value of codliver oil in rickets. However, until we really understood about vitamins, it was the habit of some men to deride those excellent clinical conclusions. It is chastening, as well as valuable, to recall the derisions with which the profession generally greeted the observations of Oliver Wendell Holmes on the transmission of childbed fever, a brilliant bit of correct observation with statistical treatment of those observations and with the resulting correct deduction.

From the very nature of things, clinical observations are complicated. Man is ever variable. Controls may be difficult. There are always unknown variables. Nevertheless, clinical material has always furnished excellent illustrations of the best and most scientific types of medical investigation. Likewise, as investigation in pure science becomes more complicated it seems to partake of some of the difficulties herein discussed. I venture this somewhat timidly and indeed humbly. I let others discuss the difference of opinion concerning the cosmic ray, concerning atomic explo-

sions, or concerning those chemical formulae that fill a blackboard only to disintegrate and reform at the waving of a chemical wand Or do they?

A great many medical beliefs, medical procedures, medical routines, and the like are based upon what we like to call the results of our logical reasoning For example, should one use ice baths to reduce fever? Obviously there are many considerations and we finally gave up ice baths as an inevitable logical procedure in fever Again, if a person is infected with a few microorganisms, is it logical to assume that he will be less sick than a person who is infected with many microorganisms? As an example, is it logical to assume that a person infected by typhoid bacilli in the water will be less sick than a person infected with typhoid bacilli in milk? Presumably the milk will carry more bacilli than the water Let us grant that the virulence of the microorganisms is the same and let us grant that the series of cases is large enough to iron out the variability of possible special groups of immunes or partial immunes The answer must be "No" of course Again, is it logical to assume that bacterial vaccines are useless in existing infection? Of course, the argument is that the living bacteria would produce immunity if it is to be produced and therefore that bacterial vaccines are useless But this illustration, like the others, concerns not the process of logic itself but the assumption of the argument It is not known whether changed bacteria, as they are in vaccines—dead, devitalized, attenuated or what not—have necessarily the identical effect in immunity production possessed by the living bacteria and indeed this may vary with different forms of bacteria and indeed in different individuals either under the same or different circumstances

Perhaps the commonest illustration concerns the prevention of the common cold by vaccine We do not know the causative agent of the common cold and therefore the bacterial vaccine used to prevent colds does not contain it and is it therefore necessarily illogical to give these bacterial vaccines as a preventive of colds? Of course, the answer must be that it is not necessarily illogical although there is no evidence that it is logical, because immunity to the cold may be produced by non-specific therapy

Some years ago, the effect of liver and other substances in the diet on the anemia in dogs secondary to bleeding was studied Of course, it had been urged that it was illogical to give meat in pernicious anemia because of the absence of hydrochloric acid Because anemia secondary to hemorrhage in dogs and pernicious anemia were quite separate entities, it seemed unlikely that liver therapy would be of benefit in pernicious anemia Of course, that happened to be exactly wrong In this case, the feeding of liver and other substances in anemic dogs was one thing and liver and allied therapy in pernicious anemia was quite another thing Or, at least, it so seems now

Everyone knows that among all individuals wishful thinking, or the rationalization of what we desire, is very common We know what we want and therefore build up arguments in its favor

One could give many illustrations of simple errors in reasoning mostly based upon the fact that in the reasoning only one instead of several possibilities are considered. The type of thing to which I refer is the reasoning that in pneumonia there is usually a high fever, therefore any high fever may mean pneumonia. Of course, such an illustration seems absurd on the face of it. On the other hand, physicians do not hesitate to argue that because appendicitis is often accompanied by a leukocytosis, therefore if there is any leukocytosis the diagnosis is appendicitis.

One hears and reads the statement that infections cause leukocytosis but with two exceptions—one, the infection may be so overwhelming that there is no leukocytosis, two, the patient may be so debilitated as not to be able to produce the usual leukocytosis. In reality, it is true different types of infections tend to produce, from the circulating toxins, etc., different effects upon the hemopoietic system and therefore different blood pictures. Some infecting microorganisms have little or no effect upon the leukocytic count, other microorganisms affect the lymphocytic system rather than the polynuclear system. Indeed, one can get results from other circulating poisons which are quite similar to the circulating toxins of microorganisms. The point is obvious, of course, that the blood picture is not in itself diagnostic of any precise disease, but indicates the effect of certain reactions on the blood-forming organs.

Again, many tests have been devised, and much time has been wasted, merely because the advocates of these tests, finding that the tests were positive in some particular disease and negative in normal people, at once concluded that the test was diagnostic of this disease. In many instances, the test is merely positive for some general type abnormality as fever. A vast amount of literature has been accumulated in regard to the so-called "blood sedimentation rate." Following the loose form of reasoning just described, the blood sedimentation rate was supposed to be diagnostic of a wide variety of conditions—pregnancy, cancer, rheumatism, etc. It was pointed out, when the sedimentation rate was being discussed in the early stages, that in normal people there was a normal sedimentation rate. In many, but not in all diseases, there seemed to be an alteration in the sedimentation rate. It was merely one of the many things that happen, the human organism is not normal. Changes in a sedimentation rate, in the same individual, may be of some value in determining the course of the disease and indeed the prognosis. After a good many years, that is the conclusion which has emerged out of a huge mass of contradictory and conflicting conclusions and summaries. Even now, undue dependence is placed upon this test, in the first place because there is no specificity about this test and, in the second place, there may be some other condition which is altering the rate besides the condition which is being studied.

In every field of medicine, one could multiply the argument for the necessity of careful and thorough deductive reasoning. As I have pointed out elsewhere, the examination of the urine is not a perfect test for nephritis.

or diabetes. Indeed, the examination of both the blood and the urine, while giving us a great deal of information, may be neither dependable nor precise. The reason for this is that the morbid processes are within the cells and the blood itself is only one step nearer the cells than is the urine. There is a good deal of evidence that the blood is used for a sewerage system and does not always reflect exactly the condition of the cell. Furthermore there may be other factors which may affect the blood and urine figures. For example, a Marathon runner will present a urine of acute nephritis. A starving patient will show a blood non-protein nitrogen which is that of uremic coma. Furthermore, if he is starving, and has enough acidosis to produce a high non-protein-nitrogen, he may also present a urinary picture of nephritis. It would be very easy to multiply these casual observations, selected at random, in the field of medical investigation but, suffice it to say, every procedure is subject to each of the factors which we have considered.

Even if we are careful of our observations, of our statistics and our logic, we must admit that many of the processes which we are studying are very little understood. From time to time that will result in seeming refutation of the value of logic. I have in mind the so-called "Wassermann" test, which is an adaptation of the complement fixation test. It was originally considered to be a specific test because, presumably, a specific antigen was used. We now know that the antigen is not specific, yet the test runs as closely to being perfectly accurate as one may expect on the law of chances. Of course, somewhere there is a reason for it. While we accept with gratitude the extraordinary accident that has given us such an extraordinarily useful test as the Wassermann test, we can use this experience as a chastening example of our fundamental ignorance and it points to the necessity of avoiding at all times a completely dogmatic viewpoint.

Hard, sound reasoning and logical deduction can be developed as a part of the necessary equipment of the medical investigator. They are as vital as accurate observation or adequate statistical data. Wishful thinking and rationalization belong to the same category of scientific sins as erroneous observations and misleading statistics. It should be and, indeed, must be the only satisfactory destiny of Medicine, to be the Science of Medicine. As such, the Science of Medicine will, we trust, be grouped with the Physical Sciences and the Natural Sciences. We like to think that we are close kin to these somewhat rigid sciences wherein data are factual and statistically adequate, and reasoning is as sound and relentless as the limitations of the present knowledge permit.

CASE REPORTS

A CASE OF ATELECTASIS OF THE RIGHT LOWER AND MIDDLE LOBES WITH BRONCHOSCOPY DEMONSTRATING SPINDLE CELL SARCOMA OF THE RIGHT MAIN BRONCHUS

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CASE REPORT

The patient, R. Z., is a 29 year old American housewife, admitted to the Second (Cornell) Medical Division of Bellevue Hospital on March 16, 1938, complaining of right-sided chest pain, cough, and 15 pounds loss of weight during the preceding six weeks.

History She had always been well, recalling only measles and chickenpox. Her mother had died of diabetes, the family history otherwise was negative. She is married, has two children living and well, having had one miscarriage. Review of her history by systems shows no relevant factors.

Six weeks before entry she developed an upper respiratory infection, diagnosed pneumonia and pleurisy by her family physician. She recovered from the acute episode, but had a persistent cough since productive of whitish sputum in small amounts, never blood tinged. She lost about 15 pounds in weight during this time. There have been no night sweats, but afternoon fever up to 102° F. was noted. She complained frequently of sharp pains in her right chest, located more often posteriorly, and worse with respiration though steady once they arose. At times she felt as though her heart were beating in her right chest but the exact date of onset of this sensation is uncertain. She has not been dyspneic, orthopneic or cyanotic.

On the morning of admission she complained once more of severe right-sided chest pain, associated with nausea and vomiting of previously ingested food. Her physician at first thought she had a minor gastrointestinal disturbance, but after persistence of the chest pain, sent her to the hospital for observation and treatment.

Physical examination On admission this thin white female appeared to be chronically ill. There was moderate pallor of the skin, conjunctivae and mucous membranes. She was not dyspneic or orthopneic, or cyanotic, but complained of severe pain and a sense of tightness in her right lower chest posteriorly. The temperature was 99.4°, the pulse rate 88, the respiration rate 24, and the blood pressure 114 mm. of Hg systolic and 76 mm. diastolic.

Important abnormalities noted were as follows. The trachea was deviated markedly to the right. There was limitation of expansion of the right chest. The heart was shifted toward the right, the point of maximal impulse being poorly felt 4 (?) cm. to the left of the midsternal line. Heart sounds were heard much better to the right of the sternum, especially those at the base of the heart, they were of good quality, with A₂ greater than P₂.

Examination of the lungs showed dullness over the upper third of the right lung field anteriorly and posteriorly, flatness over the lower third of the right chest.

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anteriorly, extending higher in the axilla and posteriorly. Breath sounds over the upper third on the right were loud, bronchovesicular, with marked increase in tactile fremitus, voice sounds, and with whispered pectoriloquy over this area. Rare post-tussive fine râles were heard anteriorly over this area. Over the area of flatness the breath and voice sounds were absent but tactile fremitus was present though markedly diminished. The left chest was normal and the remainder of the examination entirely negative.

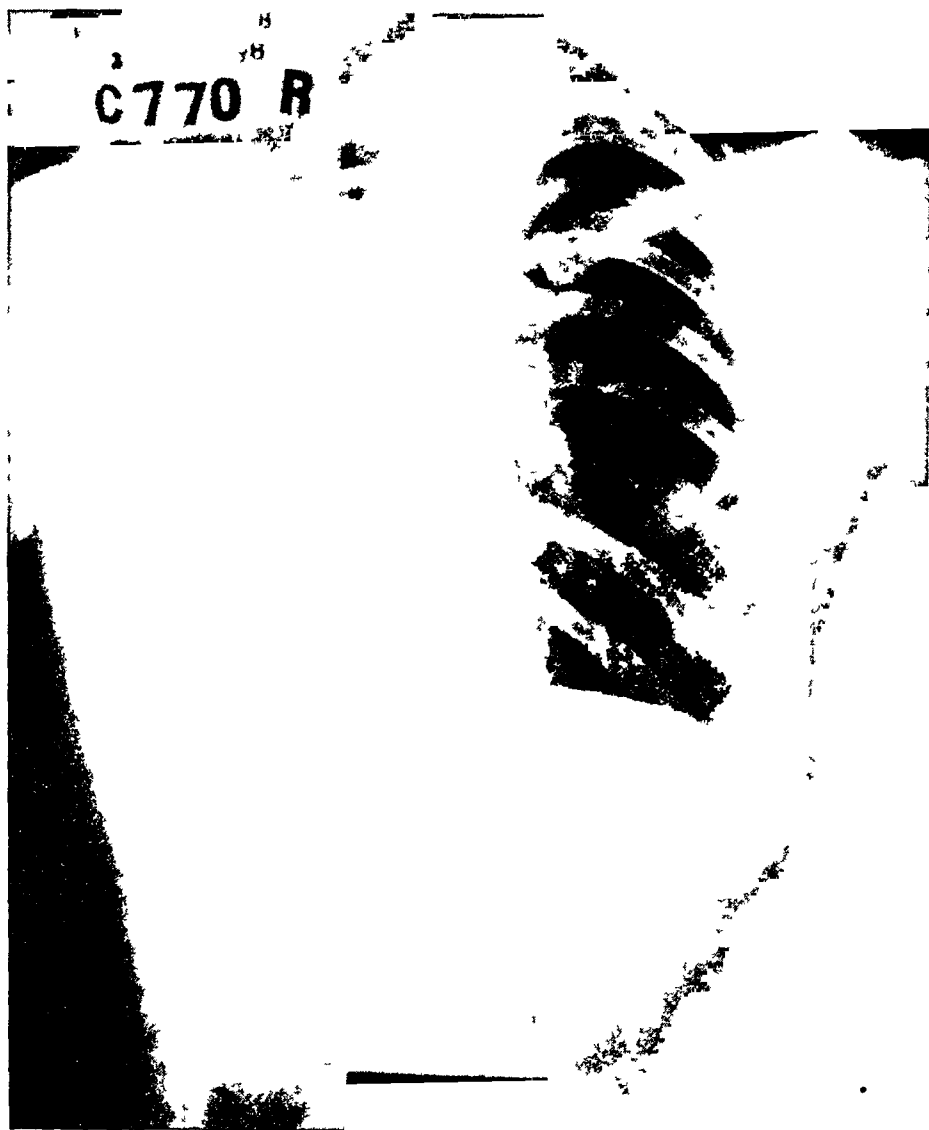


FIG 1 Roentgen-ray, March 16, showing lower two-thirds of the right lung obscured by dense shadow and heart and mediastinum drawn to the right

Laboratory findings were as follows. Urine entirely normal. White blood count 8500, a differential count showed 63 mature and 16 immature polymorphonuclear neutrophils, 21 lymphocytes and 1 monocyte. The red cell count was 4.6 millions, the hemoglobin 85 per cent (Sahli). The sputum showed no acid fast organisms. The blood Wassermann test was negative. Blood non-protein nitrogen was 31 mg per cent.

Fluoroscopy on the morning following admission showed the heart to be displaced toward the right, its left border about 1 cm beyond the left sternal margin. The trachea was deviated toward the right. The right lower lung field was completely obscured by a density having the appearance of an elevated diaphragm plus collapsed lower and middle lobes. The apex was clear (Figure 1).

It was thought that the patient had a plug of tenacious mucus or of granulation tissue in the bronchus to the right lower and middle lobes and immediate bronchoscopy

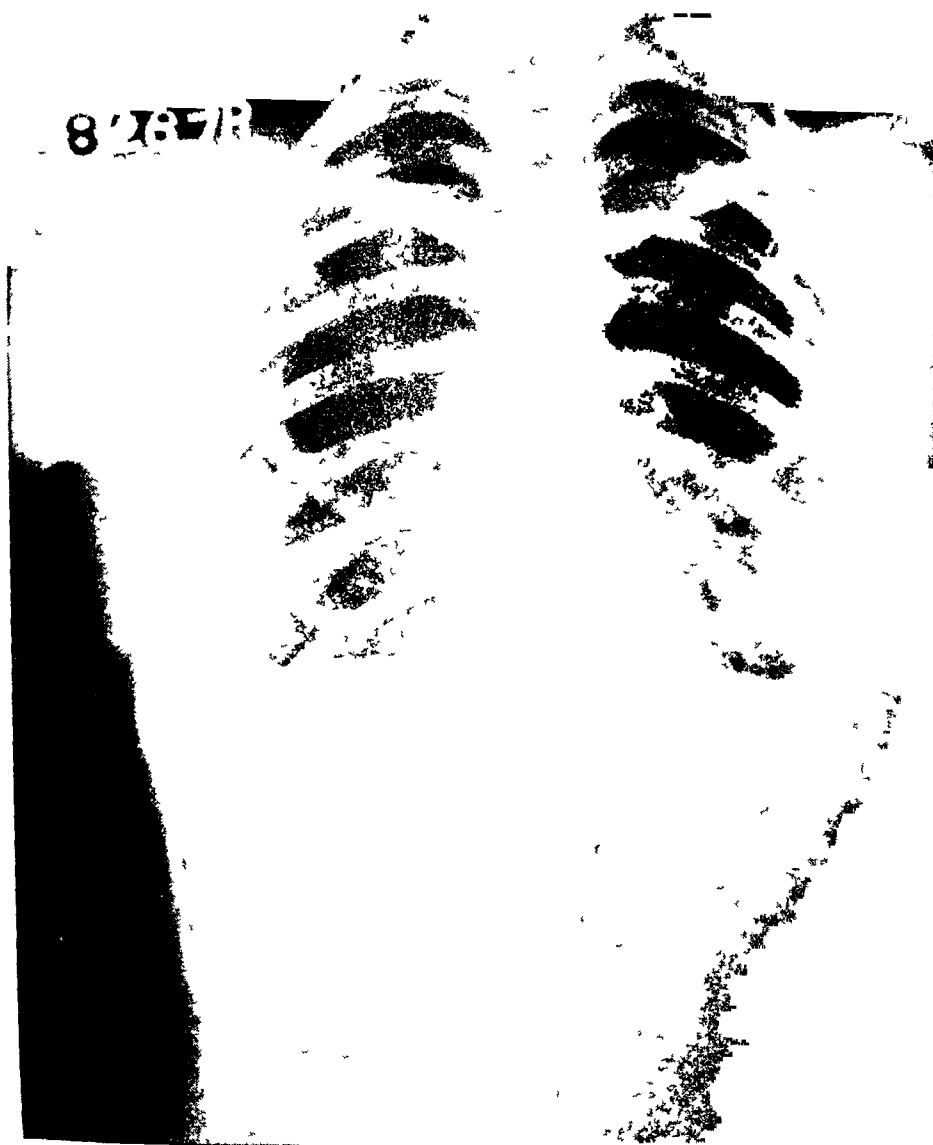


Fig 2 Roentgen-ray, March 22, showing rapid return to normal of the right chest after bronchoscopy had cleared the bronchial lumen

was deemed advisable and was performed by the Bronchoscopic Service. "The bronchoscope was passed. Just below the carina of the right main bronchus a mass of polypoid tissue, soft and friable, was seen occluding the right main bronchus. A piece was removed by forceps, the remainder being suctioned out. Air was noticed coming from the main bronchus at the conclusion of the procedure."

The patient immediately felt relieved, with complete disappearance of the chest pain, a sensation of "lightness" in the chest, and easier respirations. Three hours



FIG 3 Magnification 110 Low power microscopic view of tumor tissue

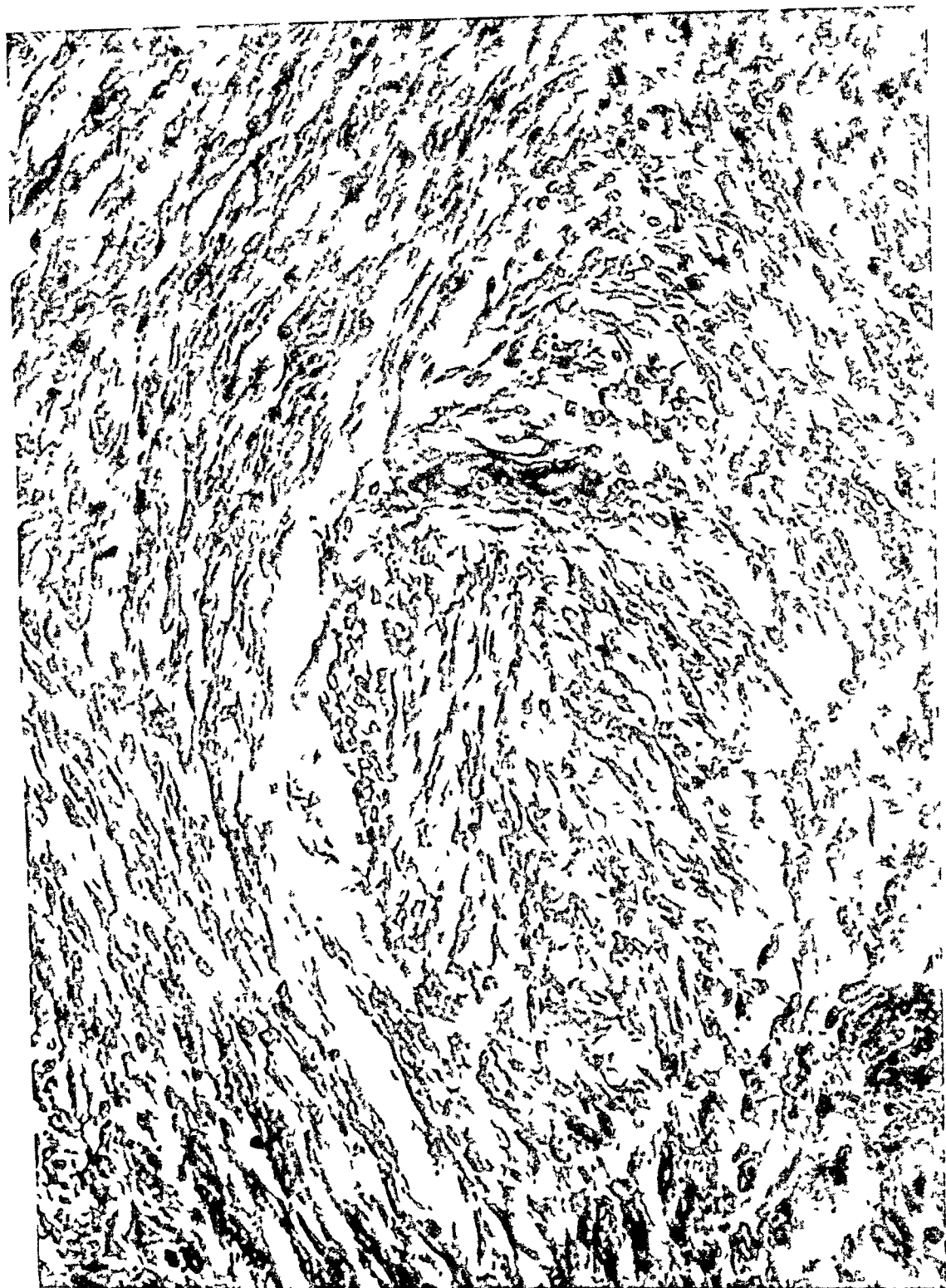


FIG 4 Magnification 390 High power microscopic view of tumor tissue

after bronchoscopy she coughed up a large mass of tissue, grayish, smooth, resembling that seen at bronchoscopy, surrounded by blood clot, in the form of a bronchial cast. Examination of the chest at this time showed a definite shift back to normal of the mediastinum, and this progressed rapidly so that seven hours after bronchoscopy the chest signs were practically absent, and 24 hours after bronchoscopy the mediastinum by fluoroscopy was seen to be in the normal position and the lungs were clear. These findings were confirmed by a roentgen film taken on the fifth day following bronchoscopy (figure 2). This state persisted throughout the remainder of the patient's hospital stay, with normal physical findings over the entire chest from 24 hours after bronchoscopy to the day of discharge.

Roentgen-ray reports March 16, 1938 "Complete obscuration of the pulmonary markings of the lower two-thirds of the right lung field. There is retraction of the



FIG 5 Bronchoscopic view, March 30, of neoplasm encroaching on the lumen of the right main bronchus (Drawing by Dr C Tannhauser)

mediastinal contents to the right. This is mainly due to atelectasis. Underlying lung pathology cannot be commented upon."

March 22, 1938 "No infiltration or consolidation of either lung. There is no evidence of neoplasm."

Pathological report The bronchoscopic biopsy, as well as section of the piece of tissue coughed up by the patient both were reported as spindle cell sarcoma (Drs Gustafson and Symmers)

"Microscopic section shows ciliated columnar epithelium, with immediately subjacent tissue consisting of dense, highly cellular fibroblastic tissue. Cell type is mainly spindle, arranged in no definite pattern" (Figures 3 and 4)

On March 30, 1938, 13 days after the first bronchoscopy, a second bronchoscopy was performed by the Bronchoscopic Service, "The bronchoscope was passed. There was a mass of tissue filling about one-third the lumen of the right main bronchus, just about 1 cm below the carina, and $\frac{1}{2}$ cm below the right upper lobe bronchus. The orifice of the right upper lobe bronchus was swollen and edematous. The mass

described was nearly all aspirated with suction. Straining of the fluid revealed a soft myxomatous mass of tissue" (Figure 5)

After consultation with the Radiation Therapy Division, deep roentgen-ray therapy to the right chest was started, and is being continued

The patient was discharged from the hospital on April 7, 1938, to return for deep roentgen-ray therapy and follow up, as well as future bronchoscopy *

COMMENT

This case is presented primarily to demonstrate the necessity for early bronchoscopic examination in bronchial lesions interfering with normal respiratory mechanics. It will be noted that the patient was bronchoscoped immediately after the diagnosis of atelectasis had been made. The dramatic and gratifying result both to the patient and the physician—even in view of the doubtful outcome in this particular case—warrants such examination.

No case report of this kind is complete without the postmortem examination, and the significance of the pathological findings is lessened by the absence thereof. However, in this case the corroboration of findings on repeated biopsies of the tumor, as well as the absence of clinical findings of a primary tumor elsewhere, seem to us to warrant its description as an intrinsic primary bronchial neoplasm.

Sarcoma of the lung is an exceedingly rare tumor. Lenk²² estimates that 0.009 per cent to, at the most, 0.02 per cent of all autopsies show this lesion. Boschowsky (quoted by Lenk²²) in 1912 in summarizing the literature up to that time found only 63 cases in the preceding 55 years. Adler in 1913 (as quoted by Pilot²⁶), found 94 cases of sarcoma reported in the literature but maintains that most of these fall into the category of round cell carcinoma. In the more recent literature, rare individual case reports are noted. Lenk, in a series of 5600 autopsies, between 1922 and 1927, found only one case. At the Massachusetts General Hospital, Mallory^{3, 4, 5, 6} reports one case in 800 autopsies, and maintains that primary fibrosarcoma of the lung is among the rarest of tumors, though pleural and mediastinal sarcomata are relatively more common, particularly neurofibrosarcomata. Ball² in reviewing the literature from 1900 to 1931, finds 13 cases of primary sarcoma of the lung. Other individual case reports are those of Davis,⁹ Roberts,²⁷ Collier,⁸ Rosenblum and Gasul,²⁸ Pilot,²⁶ Sach,¹² Jessop,¹² Heizmann,¹⁴ Otten,²¹ Herinheiser,¹³ et al. Rosenblum and Gasul²⁸ review the pediatric literature, finding, in addition to their case of a primary sarcoma of the lung in a 29 month old infant, two other cases in infants, and 11 cases in older children. Ewing¹¹ suggests that the histological appearances which inflammatory lesions, and overgrowths of reparative tissue may assume, often simulate round and spindle cell sarcomata.

Three general types of sarcoma are recognized by Lenk²²: (a) Primary sarcoma nodule—interlobar or peribronchial, (b) lobe sarcoma—involving usually the entire lobe of the lung, (c) primary sarcoma of lymph nodes.

Of these, the second is considered most frequent by Lihenthal²³. The source of the sarcoma is usually the peribronchial or interalveolar connective

* Since the time of writing this report the patient has received a course of deep roentgen-ray therapy. Subsequent bronchoscopies have revealed shrinking of the endobronchial portion of the tumor, so that the last bronchoscopy on August 17, 1938, showed merely slight elevation and reddening at the tumor site. Clinically the patient is well, and frequent fluoroscopies have shown no pulmonary or peribronchial lesions.

tissue, as well as the interstitial connective tissue of the lymph node (For purposes of clarity lymphosarcoma is not discussed) Tuffier is quoted by Lilienthal²³ as claiming that sarcomata originate usually in a bronchus, but this is disclaimed by Lenk²² The latter insists that bronchostenosis is a very rare phenomenon, that when it occurs it is due most often to external compression (cases of Frankel and of Assman) and only rarely to penetration into the bronchial lumen (cases of Kohler) For this reason atelectasis is also an uncommon occurrence

For the same reason a review of the literature revealed only one case—that of Herrnheiser,¹³ of sarcoma of the lung diagnosed by bronchoscopy (excluding one case of lymphosarcoma reported by Vinson³⁰) This is in marked contrast to the relatively frequent occurrence of benign endobronchial neoplasms of mesenchymal origin The first benign tumor removed successfully by the bronchoscopic route was an endothelioma, reported in 1917 by Chevalier Jackson¹⁶ Among other bronchoscopists reporting such neoplasms are Jackson and Jackson,^{17, 18} Jackson and Konzelmann,^{19, 20} Myerson,²⁵ Ashbury,¹ Morlock and Pinchin,²⁴ Welt and Weinstein³² In this group disturbances in respiratory mechanics resulting either in emphysema or atelectasis depending on the nature of the bronchial obstruction, are frequent The most notable in this series is the case of Ashbury¹ with three repeated massive collapses due to a benign neoplasm

The treatment of pulmonary sarcoma is naturally unsatisfactory, though considered by some to be less so than that of pulmonary carcinoma Successful lobectomies have been reported by Herzmann¹⁴ and Davis,⁹ though in the latter case recurrence was observed after two years Herrnheiser¹³ reports complete cure following deep roentgen-ray therapy of a case of an infiltrating mesenchymal neoplasm, arising probably on the basis of malignant degeneration of a polyp Implantation of radon seeds in sarcomas extending into the bronchus, as well as electro-coagulation, have been suggested, but it is well to keep in mind the case of endothelioma of Welt and Weinstein,³² which was treated by radium implantation, and which at necropsy showed a tracheo-esophageal fistula The fact that most of the cases reported are necropsies indicates the discouraging nature of the therapeutic results

In our case, deep roentgen-ray therapy was initiated after the startling discovery that in 13 days the tumor had grown sufficiently large to occlude one-third of the diameter of the main bronchus It is hoped that this method of therapy, in combination with repeated bronchoscopy and possibly electro-coagulation of the base of the tumor, will prove successful in averting the otherwise fatal outcome

SUMMARY AND CONCLUSIONS

- 1 A case of spindle cell sarcoma of the right main bronchus, with bronchoscopic demonstration of atelectasis of the right lower and middle lobes, is reported

- 2 A brief summary of the literature on sarcoma of the lung is given

- 3 Sarcoma of the lung is found to be a very rare tumor, occurring in only from 0.009 per cent to 0.02 per cent of all autopsies, endobronchial sarcoma with atelectasis is found to be rare even among pulmonary sarcomata

BIBLIOGRAPHY

- 1 ASHBURY, H E Recurrent massive collapse of the lung due to benign intrabronchial tumor, *Am Jr Roentgenol*, 1929, xxi, 452-459
- 2 BALL, H A Primary pulmonary sarcoma, review with report of additional case, *Am Jr Cancer (Suppl)*, 1931, xv, 2319-2330
- 3 CABOT CASE No 18452 Fibrosarcoma of the pleura, *N Eng Jr Med*, 1932, ccvii, 843-847
- 4 CABOT CASE No 22382 Fibrosarcoma of the mediastinum, probably neurogenic, *N Eng Jr Med*, 1936, ccxv, 558-560
- 5 CABOT CASE No 22441 Fibrosarcoma of the lung with metastases, *N Eng Jr Med*, 1936, ccxv, 837-839
- 6 CABOT CASE No 23182 Fibrosarcoma of the mediastinum, *N Eng Jr Med*, 1937, ccxvi, 798-800
- 7 CHANDLER, F G, FINZI, N S, and MAXWELL, J Irradiation treatment of malignant intrathoracic tumors, *British Med Jr*, 1934, ii, 714-717
- 8 COLLIER, H E Sarcoma of the lung, *British Med Jr*, 1931, i, 666-667
- 9 DIVIS, G Ein Beitrag zur operativen Behandlung der Lungengeschwulste, *Acta chir Scandinav*, 1927, lxi, 329-341
- 10 EDWARDS, A T Malignant disease of the lung, *Jr Thor Surg*, 1934, iv, 107-124
- 11 EWING, J Neoplastic diseases, Third edition, 1928, W B Saunders Co, Philadelphia, Pa
- 12 GRAHAM, E A, SINGER, J J, and BALIOU, H C Surgical diseases of the chest, 1935, Lea and Febiger, Philadelphia, Pa
- 13 HERRNHEISER, G Weitere Erfahrungen mit der Rontgenbehandlung maligner Bronchus- und Lungengeschwulste, *Strahlentherapie*, 1935, lii, 425-459
- 14 HERZMANN, K Über einen Fall von solitärem Spindelzellsarkom der Lunge bei einem 11 jährigen Mädchen, *Ztschr f Kinderh*, 1937, lix, 236-238
- 15 JACKSON, C Bronchoscopy and esophagoscopy, 1922, W B Saunders Co, Philadelphia, Pa
- 16 JACKSON, C Endothelioma of the right bronchus removed by peroral bronchoscopy, *Am Jr Med Sci*, 1917, clii, 371-375
- 17 JACKSON, C, and JACKSON, C L Benign tumors of the trachea and bronchi, with especial reference to tumor-like formations of inflammatory origin, *Jr Am Med Assoc*, 1932, xcix, 1747-1754
- 18 JACKSON, C, and JACKSON, C L Bronchial obstruction with special reference to endobronchial tumors, *Penn Med Jr*, 1934, xxxvii, 740-742
- 19 JACKSON, C L, and KONZELMANN, F Bronchial carcinoma, bronchoscopic biopsy in a series of 32 cases, *Jr Thor Surg*, 1934, iv, 165-187
- 20 JACKSON, C L, and KONZELMANN, F Bronchoscopic aspects of bronchial tumors with special reference to so-called bronchial adenoma, reports of 12 cases, *Jr Thor Surg*, 1937, vi, 312-329
- 21 KERLEY, P Neoplasms of lungs and bronchi, *British Jr Radiol*, 1925, xxx, 333-349
- 22 LENK, R Die Röntgendiagnostik der intrathorakalen Tumoren und ihre Differential-Diagnose, 1929, Julius Springer, Vienna
- 23 LILIENTHAL, H Textbook of thoracic surgery, 1925, W B Saunders Co, Philadelphia, Pa
- 24 MORLOCK, H V, and PINCHIN, A J S Benign neoplasms of the bronchus, with records of 9 cases, *British Med Jr*, 1935, ii, 332-334
- 25 MYERSON, M C Benign neoplasms of the bronchus, report of a case of fibrolipoma of the left main bronchus removed through bronchoscope, *Am Jr Med Sci*, 1928, clxxvi, 720-726
- 26 PILOT, I Mesenchymatous tumors of lung and pleura, *Radiol*, 1930, xiv, 391-400
- 27 ROBERTS, O W A case of pulmonary sarcoma, *Lancet*, 1931, i, 917

- 28 ROSENBLUM, P, and GASUL, B M A case of primary sarcoma of the lung in an infant 29 months of age, *Arch Pediat*, 1931, *XLVIII*, 63-65
- 29 VINSON, P P Clinical manifestations of tracheal and bronchial obstruction with certain bronchoscopic observations, *Med Clin N Am*, 1935, *XL*, 453-462
- 30 VINSON, P P Primary malignant disease of the tracheobronchial tree, report of 140 cases, *Jr Am Med Assoc*, 1936, *CVII*, 258-261
- 31 VINSON, P P, and LEDDY, E T Roentgen treatment of primary malignant disease of the tracheobronchial tree, *Ann Otol, Rhinol, and Laryngol*, 1932, *LI*, 1259-1267
- 32 WELT, B, and WEINSTEIN, S Trio of rare bronchoscopic cases, *Laryngoscope*, 1937, *XLVII*, 30-49

AN INTRACRANIAL CAROTID ANEURYSM OF LONG DURATION

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DURING the past decade, numerous articles dealing with intracranial arterial aneurysms have been published¹⁻¹² Because, with a rare exception,¹³ they have all appeared in special journals it is likely that many physicians are still unfamiliar with this not infrequent condition In 1102 consecutive necropsies (excluding stillbirths), in which the head was examined, the records of The Jewish Hospital of Brooklyn reveal 9 aneurysms of intracranial arteries This is an incidence of 0.8 per cent Other writers give an incidence of 0.5 per cent to 1.5 per cent¹⁴

Etiologically, aneurysm of the intracranial arteries may be classified as arteriosclerotic, congenital, mycotic, syphilitic and traumatic In arteriosclerosis, the uneven fatty and fibrous changes in the vessel wall probably result in weakening, bulging at some point and, consequently, the formation of an aneurysm Often, this is hastened or aggravated by the associated vascular hypertension The congenital group comprises those aneurysms which occur in young people and to which no specific cause can be assigned It is agreed by a number of observers^{9, 15, 16, 17} that these aneurysms are based upon a defect in the media of the arteries, frequently at the points of bifurcation Mycotic aneurysms are caused by inflammation of the vessel wall following the lodgment of an infective embolus from the left side of the heart Syphilis is regarded by most authors as an insignificant cause of intracranial aneurysm It cannot attack the smaller intracranial vessels through the vasa vasorum, for these nutrient channels are not present except in arteries the size of the basilar Should it affect the vasa vasorum of a vessel as large as the basilar, it might weaken the wall of the artery and permit aneurysmal formation¹⁸ In the smaller vessels the syphilitic lesion, being a productive one, usually causes occlusion rather than aneurysm In the traumatic group belong those aneurysms which follow fractures at the base of the skull or other mechanical injuries inflicted upon intracranial arteries Most of these aneurysms, being arteriovenous, are not included in this discussion¹⁹ A case of pure arterial aneurysm following a head injury in a three year old boy was included in the series of Dial and Maurer²⁰

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The clinical manifestations of intracranial aneurysm are governed by the underlying disease and by the effect upon neighboring structures. The symptoms of the underlying disease cannot, by themselves, establish the diagnosis of intracranial aneurysm. The signs evoked by changes in the neighboring structures fail, likewise, to certify the diagnosis, for most of them may be produced by any expanding lesion within the skull^{21, 22} and by certain inflammatory processes. Especially is this true before rupture of the aneurysm has occurred. It is not surprising, therefore, that the diagnosis of intracranial aneurysm was at first made only at postmortem examination, and this despite a number of reports in the early literature, among them one in 1859 by Gull of 62 aneurysms²³ and one in 1890 by Pitt of 19 aneurysms²⁴. The monumental study of Beadles²⁵ covering 555 cases and the work of Fearnside²⁶ stimulated a more lively suspicion of the lesion during life. Its diagnosis before death was proved feasible by a number of case reports^{6, 8, 27, 28, 29}.

The symptoms produced by a small aneurysm may be negligible until rupture occurs. The disturbances caused by a large, unruptured aneurysm depend upon its relation to cranial nerves or to special sites in the brain and upon whether the aneurysm irritates or destroys the structures upon which it abuts. Here, a knowledge of neuro-anatomy and physiology often serves to localize the lesion. Further and more precise evidence of intracranial aneurysm has recently been sought in roentgenographic studies, simple³⁰ or combined with endarterial injection of radiopaque substances¹¹. To Dyke³⁰ the following signs confirmed the diagnosis of aneurysm of the carotid artery: a curvilinear shadow above and slightly to one side of the sella turcica, due to calcification within the wall of the aneurysm, unilateral erosion of the sella turcica, enlargement of the sella, unilateral enlargement of the optic foramen and superior orbital fissure, erosion of the margins of the carotid canal, displacement of the pineal gland. In his series of cases no necropsies were reported.

Even when accompanied by distinct localizing signs, the vast majority of intracranial aneurysms are not diagnosed until they have ruptured. Then, the sudden hemorrhage into the subarachnoid space produces phenomena of great diagnostic value. The patient in whom rupture of an intracranial aneurysm occurs is stricken with sudden headache or severe pain in the nape of the neck and may lose consciousness. There is rigidity of the neck and a mild Kernig sign. The deep reflexes are depressed. The pupils are unequal, irregular in outline and may change their size and shape from day to day. There may be hyperemia of the optic discs or even retinal hemorrhages^{31, 32}. Slight fever and leukocytosis occur. The cerebrospinal fluid is bloody and successive portions of a single specimen are uniform in color. The blood in the cerebrospinal fluid does not clot, the erythrocytes settle out, leaving a clear supernatant fluid.

For a ruptured intracranial aneurysm, absolute rest is the safest therapeutic measure. Spinal puncture, other than the diagnostic one, is contraindicated. Cure of the unruptured or non-leaking aneurysm has been attempted, at times with success, by ligation of the carotid artery^{12, 13, 14, 33}. In untreated cases, the duration of symptoms varies remarkably between a few minutes and many years.

The following report illustrates the progress of a large aneurysm of the internal carotid artery which gave symptoms for at least 10 years.

CASE REPORT

M C, a 24-year-old white girl, was admitted to the service of Dr Irving J Sands at The Jewish Hospital of Brooklyn, on November 29, 1936, because of headache and vomiting of three days' duration and generalized convulsions one hour before admission. The convulsive movements were uncontrollable and were most prominent in the right upper extremity. She was stuporous, her temperature was



FIG 1 Aneurysm of left internal carotid artery in floor of cranial cavity, viewed from above, *a* ruptured posterior pole covered with clotted blood, *b* anterior clinoid process displaced by anterior pole of aneurysm, *c* hypophysis cerebri, *d* right internal carotid artery, *e* right oculomotor nerve, *f* left oculomotor nerve, *g* left trigeminal nerve, *h* left abducent nerve, *i* right abducent nerve

101.4° F, her pulse 84, and respirations 20 per minute. The pupils were fixed, the left much larger than the right. The vessels in the fundus of the left eye were engorged, especially at the center of the disc, and there was slight haziness of the disc margin. There was no rigidity of the neck. The superficial abdominal reflexes were not elicited, all the deep reflexes were present and there was a right Babinski reflex. The cerebrospinal fluid was pink and under a pressure of 170 mm of water. Three c.c. of fluid were removed. Shortly thereafter the patient became cyanotic. Her

pulse was weak and 150 per minute. Respirations were 10 per minute and the blood pressure was 108 mm of mercury, systolic, and 54 mm, diastolic. Her stupor deepened and she died about 35 minutes after admission. The diagnosis made was ruptured aneurysm of the left posterior communicating artery of the circle of Willis.

Subsequently, the following information was obtained from Dr. Israel Strauss of Manhattan. The patient's birth had been normal. In her infancy a slight flattening of the left side of her face was noticed. When her teeth erupted, those on

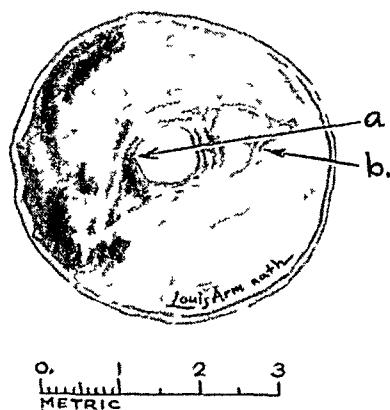
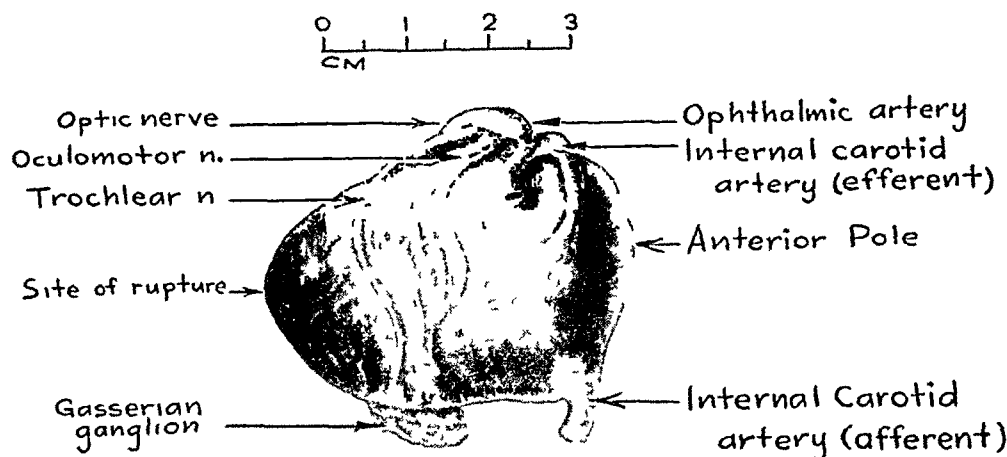


FIG 2 (Above) Aneurysm of internal carotid artery, medial aspect

FIG 3 (Below) Aneurysm of internal carotid artery, posterior pole viewed from within, *a* edge of laceration in sheath of dura mater, *b* edge of laceration in aneurysmal wall proper

the left side did not develop as well as those on the right. On exposure to cold, the left side of her face, particularly the chin, became blue. She had no serious illness until 1925, when, at the age of 13, she was in bed with the 'grippe' for two or three weeks. Following this she had occasional attacks of petit mal, consisting of momentary dizziness and clouded consciousness, with no sensation of falling and no headache. About one year later she began to see double. This always occurred when she looked to the left and sometimes when she looked straight ahead. She had no

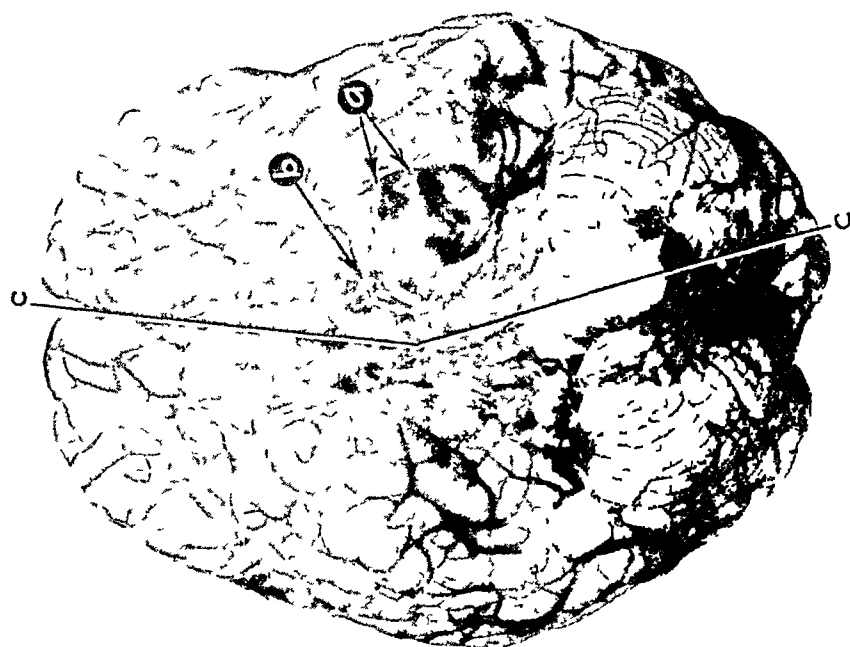


FIG 4 Brain, ventral view, after fixation, *a* sharp line of concavity in left temporal lobe, *b* left middle cerebral artery, medial to concavity, *c* angulated median axis of cerebrum and brain stem

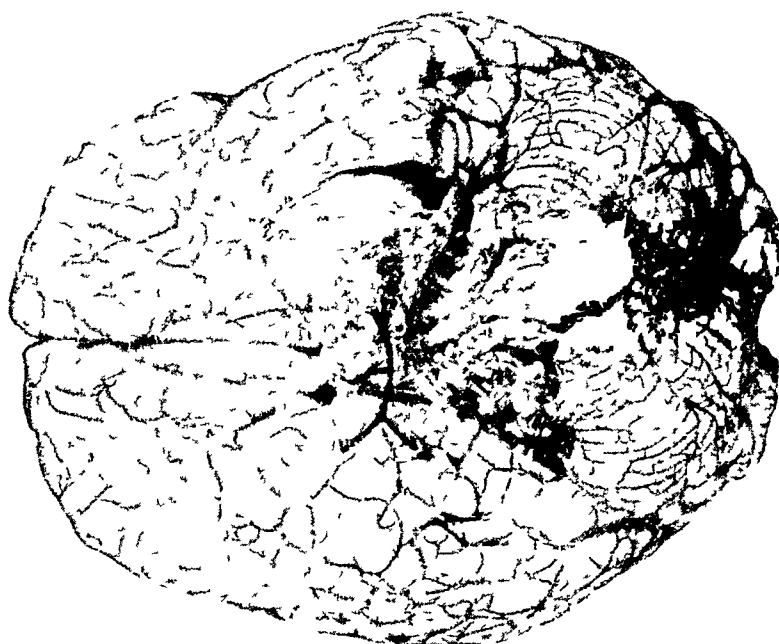


FIG 5 Brain, ventral view, with aneurysm replaced in concavity in left temporal lobe. The black thread passes through the stump of the left internal carotid artery proximal to the aneurysm. The inaccurate fit is due to shrinkage of the brain during fixation

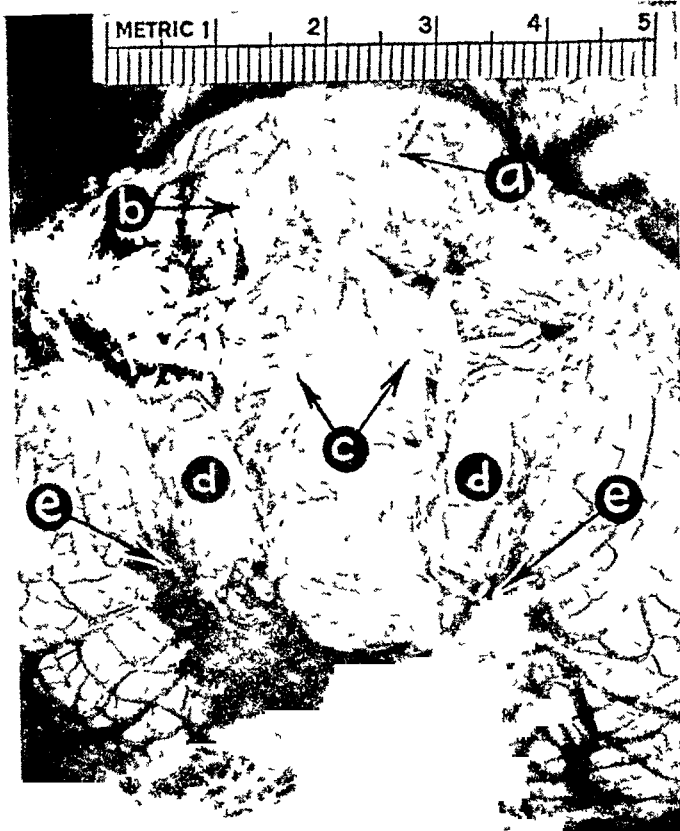
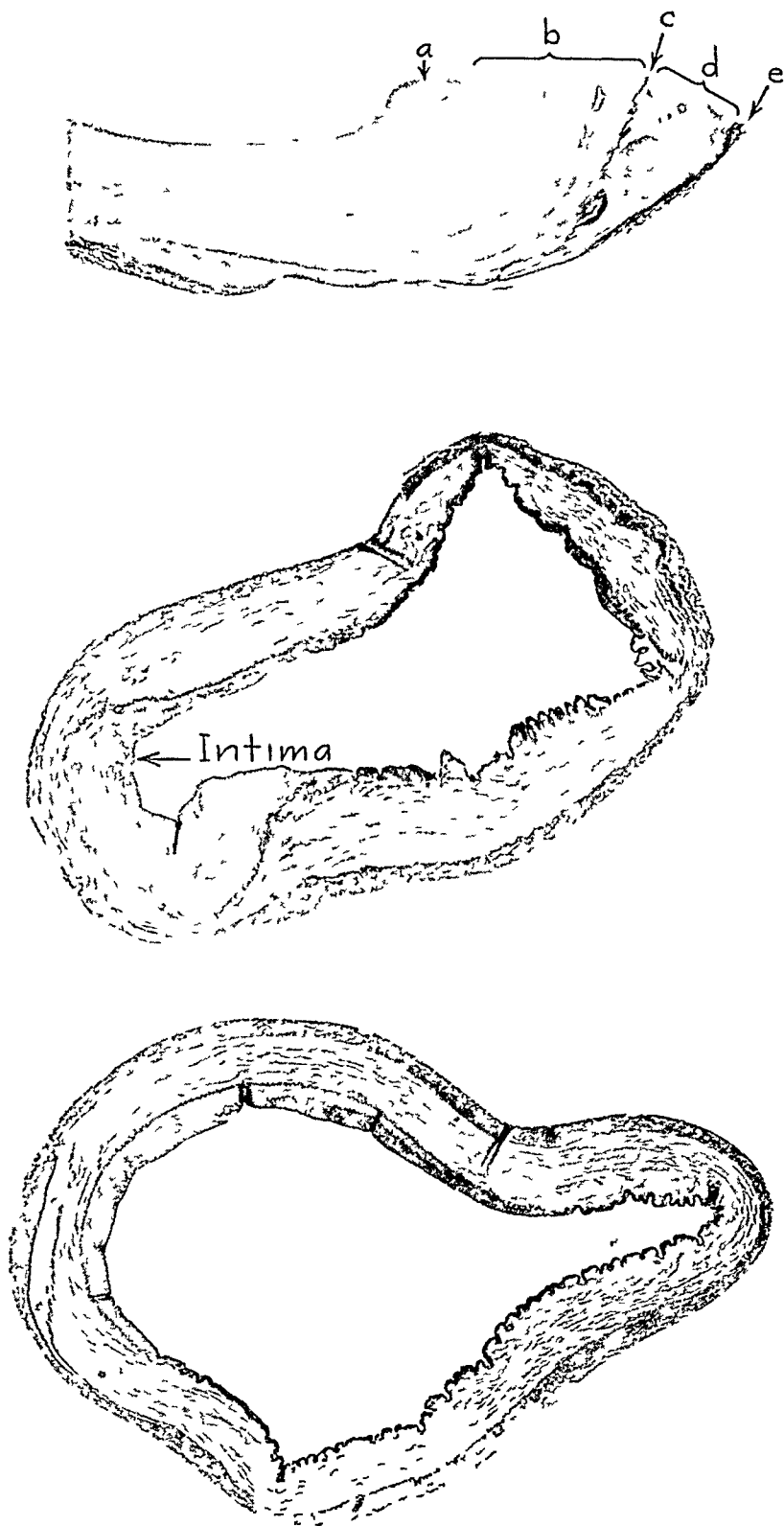


FIG 6 (Above) Hindbrain, ventral view, *a* left abducent nerve, *b* right abducent nerve, *c* vertebral arteries joining to form basilar artery, *d d* cerebellar tonsils exaggerated by pressure grooves, *e e*

FIG 7 (Below) Brain, coronal section through concavity in left temporal lobe, viewed from behind, *a* distorted pattern of compressed gray and white matter, *b* optic tracts in oblique section



FIGS 8, 9A, 9B

difficulty in reading at close range, but at the cinema, in order to avoid the double images, she sat in the left side of the theatre and kept her eyes turned to the right. Although worried by her attacks of mental confusion, she displayed no bad habits and made satisfactory progress in school.

In November 1926, roentgenograms of her skull were reported negative. On July 5, 1927, weakness of the external rectus muscle of the left eye was detected. The other eye muscles and the optic discs were normal. Two days later, Dr. Strauss affirmed the appearance of atrophy of the left side of her face. The seizures of petit mal ended after the year 1927. During the summer of 1928, the eye difficulty became worse and she saw double not only when looking to the left and forward, but also when looking slightly to the right. In November 1928, examination of her eyes disclosed complete paralysis of the left external rectus muscle and roentgenograms of her skull showed irregularity and narrowing of the left sphenoidal fissure.

She had no further complaints during the next few years and was able to maintain employment as bookkeeper and stenographer. In April 1931, Dr. Strauss noted that the right superficial abdominal reflexes were less active, and the right patellar reflex was more active than the left. Some time in 1933 the patient complained of seeing spots before the eyes, more before the left than the right. Otherwise she had no new symptoms, until November 26, 1936, when the headache and vomiting of her brief terminal illness began.

Necropsy Permission for necropsy was restricted to examination of the head. The body was 165 cm tall and weighed approximately 50 kg. Both eyes were deviated to the right, the pupils were equal, each being 0.8 cm in diameter. On the left side of the chin there was a faint purple area measuring 2.5 by 1 cm. Two lower left teeth were missing. The head was well shaped and the calvarium was of the usual thickness. There was freshly clotted blood beneath the dura mater in the left temporo-parietal region, under the left temporal lobe of the brain and about the left cerebellar hemisphere. The inferior portion of the left temporal lobe (figures 4 and 5) was compressed by, and molded over an aneurysm arising from the left internal carotid artery just above the foramen lacerum. A deep pressure groove was noted on the under surface of the cerebellum (figure 6).

The aneurysm (figure 1) formed an oval sac enveloped in dura mater, 4.5 cm long, 3.5 cm from side to side and 4 cm from top to bottom. It rested in a depression in the left middle fossa of the skull, with its long axis parallel to the ridge of the left petrous bone, and formed a broad concavity in that bone, in the left side of the body of the sphenoid bone and in the left side of the hypophysis cerebri. The left clinoid processes were spread apart and elevated by the anterior pole of the aneurysm.

The left internal carotid artery opened into the aneurysm near the junction of the anterior and middle thirds of its inferior surface and emerged from its medial aspect near the anterior pole (figure 2). At these two points the lumen of the artery was continuous with the cavity of the aneurysm. The efferent portion of the artery lay against the wall of the aneurysm and, after curving upward and backward for a distance of 2.5 cm, became the left middle cerebral artery. The left ophthalmic artery and the optic nerve were separated from the upper surface of the aneurysm.

Fig 8 (Above) Wall of aneurysm, anterior pole, *a* clotted blood, *b* thickened intima, *c* interrupted internal elastica, *d* rapidly narrowing media, *e* adventitia. Combined van Gieson and Weigert stain, magnified $\times 50$.

Fig 9A (Center) Left internal carotid artery, just proximal to the aneurysm. In one segment the intima is widened, the internal elastica interrupted and the media almost obliterated. Combined van Gieson and Weigert stain, magnified $\times 50$.

Fig 9B (Below) Right internal carotid artery, at a level corresponding to that in A. The intima in a large segment is wide and contains numerous elastic laminae, the media is unchanged. Combined van Gieson and Weigert stain, magnified $\times 50$.

by the thin posterior root of the lesser wing of the sphenoid bone. The oculomotor and trochlear nerves were compressed and spread out between the superior surface of the aneurysm and the overlying dura mater. The trigeminal ganglion, with its branches, was flattened between the inferior surface of the aneurysm and the floor of the middle cranial fossa.

There was no trace of the left abducent nerve, except for a stump one cm long, at its origin from the inferior border of the pons Varoli. This portion of the nerve was 0.1 cm thick and the corresponding portion of the uninvolved right abducent nerve was 0.2 cm thick (figure 6). The left facial nerve was not implicated by the aneurysm.

The aneurysmal sac was almost entirely filled with dark red clotted blood, easily separated from the wall. The intimal surface of the sac was smooth, gray and con-



FIG 10A (Left) Cerebral cortex, left temporal lobe. The neurons are compressed and the cellular detail obliterated. Nissl stain, magnified $\times 150$.

FIG 10B (Right) Cerebral cortex, right temporal lobe. The neurons are not distorted and the cellular detail is preserved. Nissl stain, magnified $\times 150$.

tained occasional irregular yellow areas up to 0.3 cm in diameter. The thickness of the wall varied from 0.12 cm at the anterior pole, to tissue paper thin in nearby areas. A ragged laceration 3.5 cm long and 0.7 cm wide extended across the posterior pole (figure 3). In the overlying dura mater there was a circular opening 0.5 cm in diameter, through which protruded strands of clotted blood.

The calibre of the left internal carotid artery, proximal and distal to the aneurysm, was nearly the same as that of the uninvolved right internal carotid. The other members of the circle of Willis were not unusual. The exact relationship of the left cavernous sinus to the aneurysm was not determined.

Microscopically, the wall of the aneurysm was composed of a broad intimal layer of hyalinized fibrous connective tissue, with, here and there, remnants of medial smooth muscle and elastic fibers (figure 8). Near the laceration in the posterior pole, the connective tissue fibers were frayed and spread apart by extravasated blood.

In a transverse section through the left internal carotid artery proximal to the aneurysm (figure 9A), a segment of intima, about one-sixth the circumference of the vessel, was markedly widened and the underlying media narrowed, in one area almost to obliteration. The widened intima consisted of a broad inner zone of fine connective tissue fibrils with few nuclei and a narrow outer zone with many, closely packed nuclei and some elastic fibers. Irregular clear spaces and occasional large cells with foamy or vacuolated cytoplasm and a small dark nucleus, were present in places. In a corresponding section through the right internal carotid artery (figure 9B) the intima for one half the circumference of the vessel was thickened by an increase of both collagenous and elastic fibers, the media was not altered. Preparations from other intracranial arteries were not unusual.

No distinct histologic changes were noted in myelin stains of any of the cranial nerves. In a Spielmeyer myelin stain of the pons Varoli, there was a slightly paler area in the reticular formation near the sixth nerve nucleus. In a preparation from the compressed portion of the left temporal lobe (figure 10A) the neurons were close together, narrowed, elongated and deep staining, with no distinction between the cytoplasm and nucleus.

COMMENT

In this young woman, the unheralded onset of headache and vomiting, followed in a few days by convulsions and stupor and attended by pupillary changes, indicated the presence of an expanding intracranial lesion. That it was a left sided lesion was suggested by the right Babinski reflex and the vascular engorgement of the left fundus. That it was a ruptured intracranial blood vessel was evidenced by the bloody spinal fluid under increased pressure.

One can merely speculate on the connection of the aneurysm's origin with the observations made during the patient's infancy, or with the attack of "grippe" when she was 13 years old. On the other hand, the petit mal and the diplopia point decisively to the presence of a sizeable vascular dilatation, or of a defect permitting its formation, 10 or 11 years before the patient's demise. Cessation of the attacks of mental confusion was probably due to accommodation of the brain to its early displacement or distortion. The spots before the eyes may have been caused by either a disturbance in circulation through the cavernous sinus or compromise of some fibers of the optic tracts where they pass through the white matter of the compressed left temporal lobe (figures 1, 2 and 9A). The latter is more likely, since the spots appeared before both eyes.

This aneurysm is classed as congenital because of its early onset and the absence of clinical arteriosclerosis, syphilis, endocarditis or trauma. Nevertheless, the possibility cannot be gainsaid that its origin is based upon a lesion of the artery occurring at the time of the grip-like infection. What additional information a complete necropsy would have supplied cannot be known. The structural alterations in the walls of the intracranial arteries were not specific. Those changes in the arterial wall close to the aneurysm create suspicion of a medial defect as the initial weakness, followed by the fatty and fibrous transformation of the intima.

SUMMARY

A case of intracranial arterial aneurysm is presented together with a general discussion of the subject. The aneurysm, affecting the carotid artery of a 24-

year-old woman, had given symptoms for more than 10 years and had grown to unusual size. Its origin was probably congenital.

REFERENCES

- 1 SANDS, I J Intracranial aneurysms, *Jr Nervous and Mental Dis*, 1926, *lxiv*, 12
- 2 PARKER, H L Aneurysms of cerebral vessels, clinical manifestations and pathology, *Arch Neurol and Psychiat*, 1926, *xxvi*, 728
- 3 WOLTMAN, H W, and SHIELDS, W D Neurologic complications associated with congenital stenosis of the isthmus of the aorta, *Arch Neurol and Psychiat*, 1927, *xxvii*, 303
- 4 HASSIN, G B The pathogenesis of cerebral hemorrhage, *Arch Neurol and Psychiat*, 1927, *xxvii*, 770
- 5 SANDS, I J Aneurysms of the cerebral vessels, *Arch Neurol and Psychiat*, 1929, *xxxi*, 37
- 6 SHORE, B R Intracranial aneurysms, *Arch Neurol and Psychiat*, 1929, *xxxi*, 607
- 7 PRINGST, A O, and SPURLING, R G Intracranial aneurysms their role in production of ocular palsies, *Arch Ophth*, 1929, *ii*, 391
- 8 ALBRIGHT, F The syndrome produced at or near the junction of the internal carotid artery and the circle of Willis, *Bull Johns Hopkins Hosp*, 1929, *xliv*, 215
- 9 FORBUS, W D On the origin of military aneurysms of the superficial cerebral arteries, *Bull Johns Hopkins Hosp*, 1930, *xlvi*, 239
- 10 STRAUSS, I, GLOBUS, J H, and GINSBURG, S W Spontaneous subarachnoid hemorrhage its relation to aneurysm of cerebral blood vessels, *Arch Neurol and Psychiat*, 1932, *xxvii*, 1080
- 11 MONIZ, E Intracranial aneurysm of the right internal carotid made visible by cerebral arteriography, *Rev d'oto-Neuro Ophth*, 1933, *xi*, 746
- 12 MCKENDREE, C A, and DOSHAY, L J Visual disturbances of obscure etiology, produced by focal intracranial lesions implicating the optic nerve, *Bull Neurol Institute*, New York, 1936, *v*, 223
- 13 MAGNUS, V Aneurysm of the internal carotid artery, *Jr Am Med Assoc*, 1927, *lxxviii*, 1712
- 14 SCHMIDT, M Intracranial aneurysms, *Brain*, 1931, *liii*, 489
- 15 VONCKEN, J Histological peculiarities, etiology and pathogenesis of aneurysms of arteries at base and brain, *Frankf Ztschr f Path*, 1931, *xlii*, 481
- 16 CHASE, W H Sacculated intracerebral aneurysm of middle cerebral artery, contribution to the knowledge of cerebral vascular malformation, *Jr Path and Bact*, 1932, *xxxv*, 19
- 17 DUGUID, J B Ruptured aneurysm of basilar artery at age 17, *Jr Path and Bact*, 1925, *xxviii*, 389
- 18 FRAZIER, C H Review, clinical and pathologic, of parahypophyseal lesions (Muetter Lecture), *Surg, Gynec and Obst*, 1936, *lxi*, 1
- 19 MOERSH, F P, and KERNOHAN, J W Cerebral arteriovenous aneurysms, *Jr Nervous and Mental Dis*, 1931, *lxxiv*, 137
- 20 DIAL, L D, and MAURER, G B Intracranial aneurysms, report of 13 cases, *Am Jr Surg*, 1937, *xxxv*, 2
- 21 TREVANI, E Aneurysm of internal carotid artery presenting at operation appearance of parasellar tumor, *Deutsch Ztschr f Chir*, 1932, *ccxxvii*, 534
- 22 ZOLLINGER, R, and CUTLER, E C Aneurysm of internal carotid artery, report of case simulating tumor of pituitary, *Arch Neurol and Psychiat*, 1933, *xxx*, 607
- 23 GULL, W Cases of aneurysm of the cerebral vessels, *Guy's Hosp Rep*, 1859, *v*, 281
- 24 PITT, G N The Goulstonian lectures on some cerebral lesions, *Brit Med Jr*, 1890, *i*, 829
- 25 BEADLES, C F Aneurysms of the larger cerebral arteries, *Brain*, 1907, *xxx*, 285
- 26 FEARNSIDES, E G Intracranial aneurysms, *Brain*, 1916, *xxxix*, 224

- 7 HUTCHINSON, J Aneurysm of the internal carotid within the skull diagnosed eleven years before the patient's death, *Trans Clin Soc London*, 1875, viii, 127
- 8 LEMMEL, G Three clinically diagnosed cases of aneurysm of the cerebral vessels, *Munchen med Wchnschr*, 1931, lxxix, 2193
- 9 GARVEY, P H Aneurysms of the circle of Willis, *Arch Ophth*, 1934, xi, 1032
- 0 DYKE, C G Section on X-ray diagnosis in paper of McKINNEY, J M, ACREE, T and SOLTZ, S E Unruptured aneurysm of carotid artery, *Bull Neurol Inst New York*, 1936, v, 247
- 1 RIDDOCH, G, and GOUIDEN, C On the relationship between subarachnoid and intra-ocular hemorrhage, *Brit Jr Ophth*, 1925, ix, 209
- 2 WAGENER, H P, and FOSTER, R F Ruptured intracranial aneuysm with hemorrhages into the retina and vitreous, *Proc Staff Meet Mayo Clinic*, 1935, x, 225
- 3 WALSH, M N, and LOVE, J G Intracranial carotid aneurysm successful surgical treatment, *Proc Staff Meet Mayo Clinic*, 1937, xii, 81

POLYRADICULONEURITIS, WITH REPORT OF CASE

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THE condition, variously known as infectious neuronitis, polyradiculoneuritis, polyneuritis, myeloradiculitis and polyneuritis pseudomyopathic, undoubtedly occurs more frequently than it is recognized. It appears to have been first discussed by Osler in 1892 under the designation of acute afebrile polyneuritis. Mills mentioned it in 1898 at the time the neuron theory was adopted. In 1916 Patrick noted the occurrence of facial diplegia in the syndrome of polyneuritis. In 1927 Viets mentioned the high total protein content of the spinal fluid as a diagnostic factor¹. There has been considerable discussion at times regarding its terminology, especially directed against the use of the term neuronitis, as misleading. Cobb and Coggeshall² in 1934 discussed the principal causes of neuritis at some length. They divided the generalized polyneuritides into four classes: those cases due to virus, bacterio-toxic, deficiency or metabolic, and chemical causes. Included in the virus class were such conditions as measles, smallpox, chickenpox, parotitis, herpes, acute febrile polyneuritis, acute infective polyneuritis, Landry's disease, poliomyelitis, encephalomyelitis, lethargic encephalitis, erythroedema, and acute rabic myelitis. The condition under discussion may be identified as an acute infectious generalized polyneuritis. Certain distinguishing clinical and laboratory characteristics, to be mentioned later, indicate that it is a distinct clinical entity.

Some clinical features of the condition bear considerable resemblance to anterior poliomyelitis, polyneuritis due to diphtheria or even to some of the myopathies. Some of the remarkable recoveries described as having occurred following the above conditions suggest rather polyradiculoneuritis as the condition actually present. We have seen one case of progressive muscular dystrophy (pseudo-hypertrophic muscular dystrophy) in an adult, in which, for about two years some observers had held that the condition was due to infectious neuronitis. The persistent and progressive advance in the symptoms and physical findings in this case, together with the presence of marked muscular atrophy, however, proved the condition to be one of muscular dystrophy.

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The actual etiology is not definitely known. In a certain, possibly the larger number of cases, there has been an acute infection, frequently of the upper respiratory tract, present for several days to several weeks prior to the onset of the disease. Some writers mention various other factors which are noted in other forms of multiple neuritis as possible etiological factors in this condition, such as poisoning with the heavy metals, including gold, avitaminosis, alcohol, barbitol, emetine and syphilis. The theory of a virus as the etiological factor finds considerable favor. While the disease may occur at any age it is more frequently present in adults. The onset may be fairly sudden, with weakness and paresthesia of the extremities, generally more marked in the lower. There is usually some disturbance of sensation but this is not marked. The muscles of the face may be involved and even the cranial nerves, although the latter are generally intact. Sphincter control is not affected as a rule. Severe pain is occasionally present, but is not noted in other cases. Ordinarily there is no fever. The characteristic features are the rather rapid and widespread involvement of all the extremities in a flaccid paralysis, of varying degrees of severity, with little in the way of other clinical or laboratory findings to account for the condition. The characteristic laboratory finding is an increase in the total protein of the spinal fluid with a normal or but slightly elevated cell count, a slight increase in globulin and a colloidal gold of the meningitic type, any increase of cells being of the lymphocytic variety.

The paralysis tends to increase steadily and may be so extensive as to render the patient entirely helpless. The deep reflexes are diminished or absent, no fibrillation is noted in the muscles and no atrophy other than may arise late in the disease as a result of disuse. There is frequently some muscular pain and tenderness. Choking of the optic discs occurs in some cases. Of 20 cases reported by Gilpin, Moersch and Kernohan¹ the total protein of the spinal fluid varied from 100 to 800 milligrams per 100 c.c., increasing steadily during the early period of the disease, as did the cells, which averaged 12 lymphocytes per 100 c.c. of fluid. The colloidal gold in their cases was mid-zone in 50 per cent and first zone in 25 per cent, the sugar and chloride of the spinal fluid were normal.

Abadie, Bergouignan and Verger² noted a slow onset in some cases and remarked that it was not unusual to note fibrillary tremors in the muscles after light percussion. They found also that marked pain may be present throughout the extremities, paroxysmal in severity, but the pain later disappears, leaving only tenderness to pressure over the muscles and perhaps the peripheral nerves. A case which these authors reported showed a marked intensity, with extension to all the masses of skeletal muscles, of fibrillary tremors, which were incessant, they believed that these tremors were evidence that the infectious process was not limited to the peripheral nerves, that it was a question not of a pure polyneuritis, but a diffuse infectious celluloneuritis.

Pathologically, the affected peripheral nerves show degenerative changes without any evidence of an inflammatory reaction. There is also involvement of the dorsal root ganglia, with lymphocytic infiltration. The pathologic changes may extend to the spinal cord and to the brain, they are patchy in distribution.

While the clinical picture is generally quite uniform the disease may be mild and of short duration, long and severe or fatal. H. D. McIntyre⁴ separates the cases into four groups from a clinical standpoint.

- (1) Group with rapid onset, with rapid recovery, usually with some evidence of seventh nerve paralysis
- (2) Group with steady downward progress with early death
- (3) Group with long drawn out course, with incomplete recovery
- (4) Group with long drawn out course, terminating in death, usually from heart failure, bulbar or respiratory paralysis

The diagnosis is based on the history of the preceding illness and a latent period of well being, then the development of the polyneuritis. There may be involvement of the cranial nerves with facial palsy, or choking of the discs. The increase of total protein in the spinal fluid, with but slight change in the cell count, is the diagnostic laboratory finding. This finding is possibly not always present, especially at the time the patient is seen as it may be transitory and its absence late in the disease, if the patient is first seen then, would have little diagnostic significance, either negatively or affirmatively. The electrical reaction of the affected muscles is always that of degeneration, more frequently incomplete, the changes being most marked in the muscles of the extremities, scapular and pelvic girdles and anterior abdominal wall³. The reaction may appear also in muscles which are clinically not affected.

The differential diagnosis includes anterior poliomyelitis, Landry's paralysis, diphtheritic paralysis and certain of the myopathies. In anterior poliomyelitis the markedly rapid onset and progression, with fever, leukocytosis, with polymorphonuclear increase and the pleocytosis of the spinal fluid are indicative of this disease. In Landry's paralysis the rapid onset and progression, generally from the lower extremities upward, with absence of increase in the total protein of the spinal fluid and usually an early fatal termination, should suffice for differentiation. In the myopathies, aside from the hereditary family character of the affection, the onset is one of marked slowness, without any initial infectious episode and while the muscle reflexes are abolished tendon reflexes do not disappear until late, also there are no sensory disturbances. The cerebrospinal fluid is normal and the electrical reactions are not those of degeneration. In infectious polyradiculoneuritis the changes in the motor cells of the spinal cord, in the nerve roots and posterior ganglion cells, and the secondary rôle played by peripheral lesions differentiate the condition from ordinary peripheral neuritis. According to McIntyre the albumino-cytologic dissociation in the spinal fluid differentiates infectious neuronitis from the toxic neuritides, in which the globulin is never so greatly increased while toxic neuritis, such as that due to alcohol and arsenic, shows a more peripheral character of the neuritis and lacks the albumino-cytologic dissociation. He warns against overlooking a previous diphtheritic infection as an etiological factor.

While recovery is the general outcome in this disease, death in the more severe cases, especially from respiratory failure, is not infrequent. The acute stage is generally from one to three months in duration, the entire course of the illness lasting from a few months to two and one-half years. Usually recovery is complete, there being no residuals of any nature, this is in contra-distinction to the true myopathies where permanent damage is to be expected.

The treatment is entirely symptomatic, complete bed rest is of the first importance, attention to elimination, a high vitamin diet, with especial attention to vitamin B₁, assurance of an adequate fluid intake, and sedation as required.

for the pain, are obvious measures. Later in the disease gentle massage, baking and other mild physiotherapy measures may assist in a more rapid return to normal of the affected muscle groups. Electricity, per se, as a form of treatment has no place and may possibly do harm in the early stages. Good nursing and attention to the eyes and dental hygiene should not be neglected. Because of lacrimation, drooling from inability to swallow well and the patient's inability in certain cases to help himself in any way, a special attendant is required.

CASE REPORT

An interesting case of the above condition, occurring in a white male, aged 19 years, and showing extensive involvement, including the cranial nerves, was admitted to the hospital at Fort Sam Houston, Texas, on October 29, 1937. The family history and previous personal history were unimportant. The patient denied the use of alcohol (except occasionally beer) and tobacco. He denied all forms of venereal disease. The onset of the present illness had been noted one week previously, in the form of progressive weakness in both legs. There was no history of any previous acute infection or of any other illness. The patient stated that the first symptom noted was numbness and coldness of the toes of both feet, about 24 hours later he noticed difficulty in stooping to lift a small package from the ground and he had to rest at frequent intervals while on duty as a night watchman. On the second day following he noted pain in the right temple, extending across the forehead. There was no dizziness. Later that same day there was some difficulty in swallowing. He reported sick and was placed in bed, his temperature was normal. On the following day there was considerable difficulty in swallowing, his legs had been getting progressively weaker and at this time he was unable to lift them from the bed. After three days in the CCC Infirmary he noticed that his arms had also become weak and that there was numbness in his finger tips, his right arm being weaker than the left. There was severe pain in the temples almost constantly at this time. On the fifth day of his illness, and while still at the Infirmary, he fell to the floor and could scarcely arise, he could stand on his feet but could not walk. Upon his arrival at the hospital at Fort Sam Houston, Texas, seven days after the onset of his illness, he was unable to sit up because of muscular weakness and there was a flaccid paralysis of both lower extremities. There was also considerable weakness of the muscles of both arms and of the face, he had marked difficulty in swallowing and could scarcely raise his head from the pillow.

Physical examination showed a well developed young adult male. He had an anxious, worried facies, was well nourished. Vision, hearing and smell were normal. The fauces and pharynx were reddened and granular, the tonsils also were reddened and engorged. The pulse was full and a little rapid. The heart and lungs were negative on examination. Blood pressure 124 systolic and 78 diastolic, right arm, in millimeters mercury, the patient being recumbent. External genitalia normal. Bones and joints normal. The pupils were equal, regular in outline and reacted but sluggishly to light. The eyes moved freely in all directions, there was no diplopia and no definite ptosis noted at this time. The left seventh cranial nerve showed marked weakness and the left eyelid did not close completely. The tongue deviated to the right. The pharyngeal muscles showed weakness, liquids regurgitating through the nose when he attempted to swallow. All of the deep reflexes were markedly decreased, and the cremasteric and abdominal reflexes were absent bilaterally. The patient complained of paresthesia in the left arm and leg, tactile acuity was diminished in the right arm and leg. The joint and vibratory senses were normal, there was no clonus or Babinski, no muscular fibrillation and no disidiokokinesis. He complained of pain in the right side of the skull, anteriorly, present for the past week. Although obviously acutely ill the temperature was normal. He was unable to move

the lower extremities and there was marked weakness in both upper extremities, so much so that he was unable to care for himself in any way. He was mentally clear.

Soon after admission to the hospital he developed bilateral facial paralysis, with increased weakness of the pharyngeal muscles. Tube feeding was required for a period of more than two weeks. There was considerable respiratory difficulty, due to involvement of the diaphragm and of the accessory muscles of respiration. He had increased lacrimation, bilaterally, and inability to close either eye, he drooled considerably, there being apparently some increased secretion, together with inability to swallow well. His temperature remained normal throughout his illness and he was always clear mentally.

The electrocardiogram showed sino-auricular block with ventricular escape. The cardiac rate during the first few weeks of his hospitalization ranged from 98 to 144 per minute. Roentgen-ray of the chest showed the heart and lungs to be negative.

The paralysis of the upper extremities soon became more marked, especially in the proximal groups of muscles, the patient being unable to elevate the arms at the shoulders, although there was some power of flexion at the elbows. Electrical tests of the involved muscles failed to demonstrate any reaction of degeneration. The muscles of the upper extremities responded normally to the faradic current. All the muscles of the lower extremities responded to the faradic current, except the *peroneus brevis* and *extensor digitorum brevis* but some of the responses were weak, as in the *abductor longus*, left, *vastus externus*, left, *extensor communis digitorum*, left, *extensor hallucis*, left, *rectus femoris*, right, *peroneus longus*, right, *tibialis anticus*, right, and *extensor hallucis*, right. All the muscles which were weak on faradic responses responded normally to the galvanic current.

The eyes, including the lens, media and fundi, were normal, the discs being clearly defined and showing no elevation.

The white blood count on the day following admission showed 7,900 cells with 72 per cent neutrophiles, on November 13, 10,600 cells with 82 per cent neutrophiles. The red blood cells and hemoglobin were normal. The blood Wassermann and Kahn were negative. Repeated urine specimens were negative with one exception when albumin, a few white blood cells and a few finely granular casts were noted. A spinal fluid specimen taken at the time of his admission to hospital was practically negative, there were 5 cells, a very slight trace of globulin and the colloidal gold was 1 2 2 2 2 2 1 0 0, the Wassermann was plus minus in the 1 c c specimen, negative in the others. The sugar content was 73.5 milligrams per 100 c c, the pressure was 5 millimeters of mercury. Seven specimens of spinal fluid taken subsequently over a period of six weeks showed about the same findings, except that the Wassermann was always entirely negative, the highest cell count noted was 7 cells, the globulin was always slightly positive, the pressure varied from 5 to 6 millimeters of mercury, the sugar content was 67.1, 68.9, 61.7 and 63.3 per 100 c c fluid. The colloidal gold was 4 4 4 4 2 2 1 1 0 0, 4 4 4 4 3 2 2 0 0, 2 4 4 2 2 2 1 1 0 0 and 0 0 1 2 1 0 0 0 0 0. The culture of the spinal fluid was repeatedly negative. The total protein content of the spinal fluid, however, showed the alteration generally considered as diagnostic of polyradiculoneuritis, that is an increase which rose from 18.4 milligrams per 100 c c to 122 milligrams, the height of the curve being on November 26. The curve then gradually decreased to normal (15 to 45 milligrams considered normal).

The blood chemistry (sugar, urea nitrogen, CO₂) soon after admission showed a slight increase in urea and a slight decrease in the CO₂ combining power. The throat culture at the time of admission showed a heavy infection with *Streptococcus viridans* and some Vincent's organisms, later hemolytic streptococci were found in considerable number in the throat smear.

The patient was discharged on March 22, 1938, approximately five months after admission. At that time he was ambulant, capable of taking moderate exercise, the difficulty in swallowing and tachycardia had entirely disappeared. His muscular strength had practically returned to normal, yet there was still some weakness and lack of endurance. Reaction to the faradic current was practically normal. Patient stated he felt quite well and recovery was apparently complete.

This case was a rather unusual one in that the vagus, bilateral facial, and pharyngeal nerves were involved, in addition to the generalized spinal involvement. This patient's electrocardiogram had returned to normal prior to his discharge. The fact that the total protein in the spinal fluid was not as much increased as is frequently seen and the relatively short period of illness would indicate a pathologic process of moderate intensity in spite of the massive involvement. We were unable to locate any reference in literature to vagus involvement in this condition. The findings as a whole were quite typical.

- a* The extreme involvement in the cerebral and spinal nerves, with minimal sensory changes
- b* The afebrile course
- c* Normal blood picture
- d* Normal cerebrospinal fluid, except for the increased total protein
- e* The lack of atrophy in the involved muscles
- f* Complete recovery

Although the patient denied any previous illness of any kind, a focus of infection in the throat as a possible etiologic factor is to be considered, in view of the finding of streptococci in considerable numbers at the time of his admission to the hospital.

REFERENCES

- 1 GILPIN, S. F., MOERSCH, F. P., and KERNOHAN, J. W. Polyneuritis, a clinical and pathological study of a special group of cases frequently referred to as instances of neuronitis, *Arch Neurol and Psych*, 1936, **xxxv**, 937-963
- 2 COBB, STANLEY, AND COGGESHALL, H. C. Neuritis, *Jr Am Med Assoc*, 1934, **ciii**, 1608-1610
- 3 ABADIE, BERGOUIGNAN and VERGER. Polyneuritis pseudo-myopathic, *Jr Med Bordeaux*, 1936, **xxxii**, 785
- 4 MCINTYRE, H. D. Infective neuronitis, *Ohio State Med Jr*, 1937, **xxviii**, 875-883

EDITORIAL

SULFANILAMIDE AND THE BLOOD

It is extremely unfortunate that the administration of sulfanilamide, which has proved so valuable in the treatment of certain bacterial infections, should give rise to such a variety of toxic manifestations in human beings. The most serious of the toxic effects that have been observed to date are those upon the peripheral blood and the hemopoietic system, to wit acute hemolytic anemia and granulocytopenia. The cyanosis so commonly noted during the course of sulfanilamide therapy may at times be due to methemoglobinemia, but in most instances it is apparently caused by the formation of some colored compound which is of no particular clinical significance.

Some time before Harvey and Janeway¹ published their initial report on three cases of acute hemolytic anemia following the use of sulfanilamide, it had been postulated by hematologists that the drug might be expected to produce agranulocytosis and other forms of blood dyscrasia on the basis of its chemical structure involving the benzamine linkage. Since the original communication of Harvey and Janeway, a number of cases of acute hemolytic anemia have been recorded both in this country and abroad. In his recent review of a series of 522 patients treated with sulfanilamide Wood² found that acute hemolytic anemia developed in 21 or 4 per cent. It is of interest that the incidence among the 144 children included in the series was 8.3 per cent in contrast to 2.4 per cent among the 378 adults.

This acute hemolytic anemia following sulfanilamide presents a well-defined clinical picture, characterized by fever, malaise, jaundice, a rapid fall in the erythrocyte count and the hemoglobin level, a moderate to marked leukocytosis, marked reticulocytosis, hyperbilirubinemia, urobilinuria, and in certain instances porphyrinuria. In a few cases evidences of hemoglobinuria and hemoglobinemia have been noted. Signs of hemolysis are usually recognizable within 24 to 72 hours after the administration of the drug has been started, and the maximal anemia generally develops within three days after the hemolytic process is initiated. The hemoglobin level may drop from a value of 90–100 per cent to as low as 20–30 per cent in an amazingly short period of time. The leukocyte count may rise to a level of 60,000 to 100,000 white blood cells per cubic millimeter. The blood smear shows signs of sudden stimulation of the bone-marrow with the outpouring of many immature cells of the myeloid series in addition to large numbers of nucleated red cells and reticulocytes. The fragility of the erythrocytes in saline solutions has been normal in the cases reported so far. The clinical features and blood changes in this type of hemolytic anemia are

¹HARVEY, A. M., and JANEWAY, C. A. The development of acute hemolytic anemia during the administration of sulfanilamide (para-aminobenzene-sulfonamide), *Jr Am Med Assoc*, (July 3), 1937, *cix*, 12–16.

²WOOD, W. B., JR. Anemia following sulfanilamide therapy, *Jr Am Med Assoc* (in press).

very similar to those found in two other forms of acute hemolytic anemia, the acute "idiopathic" hemolytic anemia of Lederer and the hemolytic anemia of favism. The latter is very rare in this country but quite common in southern Italy. It is apparently caused by a toxic substance present in the fava bean to which certain individuals, frequently several members of the same family, become in some way hypersensitive. Ingestion of the bean is followed by an acute febrile illness accompanied by jaundice and severe anemia.

The mechanism of the production of hemolytic anemia by sulfanilamide is not understood. There is no evidence that any one type of infection predisposes an individual toward this form of anemia. The size of the dose does not appear to be of much importance, for many individuals tolerate large doses of the drug over long periods without developing anemia. Furthermore, there was no correlation between the level of sulfanilamide in the blood and the development of acute anemia in Wood's series of cases. Individual idiosyncrasy undoubtedly is a major factor, for a very small percentage of patients treated develop the acute anemia and, as Wood has shown, once an individual has developed an acute hemolytic anemia the chances are very great that he will suffer a recurrence of the anemia if a second course of sulfanilamide is administered, even as long as a year after the initial course of therapy. Various theories have been propounded as to the mechanism by which hemolysis is induced. One of the most plausible of these is the suggestion that in the affected individuals a portion of the sulfanilamide may be converted in the body to a hemolytic compound. Attempts to reproduce the anemia experimentally in animals have met with failure up to the present.

Fortunately few fatalities have resulted from hemolytic anemia so far, for the hemolytic process, if recognized sufficiently early, can be halted as a rule by the immediate discontinuation of the drug, the administration of large amounts of fluid to rid the body of sulfanilamide as rapidly as possible, and one or more blood transfusions. The pathologic findings in the one fatal case that has been reported³ were regarded as being representative of any severe acute hemolytic anemia. There was hemosiderosis of the liver, spleen, and kidneys, hyperplasia of the sternal and vertebral marrow with normal fatty femur marrow. The renal tubules contained some hemoglobin casts and the sections of the kidneys were said to resemble those from cases of black-water fever except for the absence of malarial pigment. No pathologic feature was noted which could be considered to be a specific lesion produced by sulfanilamide.

The other serious complication of sulfanilamide therapy, granulocytopenia, appears to be much less common than acute hemolytic anemia. Wood noted only one case of agranulocytic angina among the 522 patients in his series, and this patient made a prompt recovery after the medication was

³ Wood, H. A fatality from acute hemolytic anemia which developed during the administration of sulfanilamide, *Southern Med Jr*, (June) 1938, xxvi, 646-649.

stopped. However, a number of fatal cases have been reported from widely scattered points. Kracke⁴ in his excellent review of the relation of drugs to neutropenic states has collected 11 cases of granulocytopenia following the administration of sulfanilamide or one of its derivatives, nine of these cases were fatal. He has pointed out that with the dissemination of knowledge regarding the danger of granulocytopenia from aminopyrine the number of cases reported annually as due to this drug has greatly diminished, especially in Denmark where the use of aminopyrine has been curtailed by law. Kracke predicts that sulfanilamide will gradually replace aminopyrine as the foremost cause of granulocytopenia. The clinical and pathologic picture of granulocytopenia following sulfanilamide appears to be identical with that following aminopyrine. Once more it is evidently a matter of idiosyncrasy in the occasional patient. The mechanism of production of the granulocytopenia associated with maturation arrest in the bone-marrow is still a complete mystery.

It is of the utmost importance that physicians employing sulfanilamide in the treatment of the various acute infections be acquainted with the dangers inherent in the drug. In order to prevent the development of a serious hemolytic anemia or granulocytopenia it is urged that every patient receiving sulfanilamide should have a hemoglobin determination and a leukocyte count at least every second day. The urine should be frequently examined for urobilin. Unexplained fever, developing during the course of sulfanilamide therapy, should be regarded as a warning sign that some more serious toxic effect may be imminent. Obviously, proper supervision of the patient is only possible if he is under the constant care of a physician and preferably in the hospital. The new Food, Drug, and Cosmetic Act prohibits the sale of sulfanilamide to the public in "patent medicines." It would be even more desirable to make such drugs as sulfanilamide and aminopyrine available to the public only upon the prescription of a licensed physician, who would assume full responsibility of the care of the patient throughout the course of therapy.

⁴KRACKE, R. R. Relation of drug therapy to neutropenic states, *Jr Am Med Assoc*, (Oct 1) 1938, *cvi*, 1255-1259.

REVIEWS

Chemistry of the Brain By IRVING H. PAGE, M.D. xvii + 444 pages, 17.5 × 26 cm
Charles C. Thomas, Springfield, Illinois 1937 Price, \$7.50

According to the author this book was written in the belief that chemical investigation is essential to the development of psychiatry. It represents an up-to-date summary of our knowledge concerning brain constituents and their metabolism. Various chapters are devoted to the biochemistry of the sterols, phosphatides, cerebrosides, fatty acids, carbohydrates, proteins, inorganic elements and gases with particular emphasis upon the activity of these substances in the brain. Certain phases of physical, enzymatic, vitamin and comparative neurochemistry are given adequate consideration including a chapter on oxidations and reductions contributed by J. H. Quastel of the Cardiff Mental Hospital. In addition the clinical aspects of this subject have not been neglected.

Of interest and value is a short historical survey of the life and work of Thudichum and of the genesis of brain chemistry.

There are full references not only to the journal literature but to the leading books, monographs and reviews dealing with this subject. The book has an element of authority due to the fact that the author has been a frequent contributor in this field of research. It will be welcomed as an invaluable source of information to all investigators interested in the chemistry of the brain.

E. G. S.

Diseases of the Blood By CARL C. STURGIS, B.S., M.D., and RAPHAEL ISAACS, A.B., A.M., M.D., Edited by MORRIS FISHBEIN, M.D. National Medical Book Co., Inc., New York, N.Y. 1937

This small handbook will be of considerable value to the medical student and to the general practitioner. It presents in a brief clear way the chief data relating to the principal diseases of the blood. If all that is in this book is well digested the physician will be better informed than the average of his fellows. The feat is fairly easy of accomplishment. If, however, the student or physician did not learn elsewhere more concerning the formation and the destruction of blood and the part they play in the pathology and symptomatology of blood diseases than is contained in this manual he would have little insight into the pathogenesis of blood diseases. The reviewer feels that the monograph produced by Dr. Sturgis and Dr. Isaacs is a very valuable brief summary furnishing an easy method for brief review of the clinical aspects of blood diseases. A few more references would add to its value.

M. C. P.

Martini's Principles and Practice of Physical Diagnosis Edited by ROBERT F. LOEB, M.D. 213 pages, 13 × 19.5 cm. J. B. Lippincott, Philadelphia 1938 Price, \$2.00

This small volume covers the entire field of the principles and the practice of physical diagnosis. The preface to the first edition points out that only the important "physical signs" are included and that many signs, while still in usage, have been omitted because of the development of more accurate and indispensable aids to diagnosis. The fulfillment of this intent should then lead to simplicity and clarity, and if the volume fails in these scores it is not because of the lack of content, but rather because of the arrangement of the material. The student or the beginner in the study of physical diagnosis will be hard put—in the reviewer's opinion—to gain a clear

concept of the principles underlying the physical diagnosis of the respiratory system from study of this work. Of more value to the beginner will be the sections on the circulatory system and the abdomen. These sections are clearly arranged and discussed and are the more valuable parts of Martini's work.

The first section of the book confines itself to the observation of the patient and here the author has stressed many important details. Included in the first section are some notes on the subject of acoustic diagnosis, this addition seems aside from the general purpose of the book. The discussion of the principles of palpation, percussion and auscultation is not as clear as might be desired.

The second section is a detailed description of the physical diagnosis of the respiratory system and it is in this part that Professor Martini's book is weakest, not because of lack of material but because of the manner of presentation.

The section devoted to the physical diagnosis of the circulatory system is well arranged and well worth the close attention of the reader. The same may be said of the section on the examination of the abdominal organs. The observations and the descriptions are quite clear.

A detailed outline of a medical history completes the book. This outline is well done and the form is similar to that generally used by the medical profession.

Dr Martini has compiled a small, but within its limits, a complete treatise on the principles and practice of physical diagnosis. All of the pertinent facts are presented. The book can well take its place as one that may be used by elementary students of physical diagnosis.

M J

Chronic Intestinal Toxemia and Its Treatment By JAMES W WILTSIE 268 pages
William Wood and Co, Baltimore 1938

The author of this monograph has made many contributions to the literature of colonic irrigations and is as well fitted as any physician to present the point of view of those who stress the importance of intestinal toxemia and who believe in the efficacy of colonic lavage as a form of treatment. There has been no doubt a good deal of prejudice for and against this point of view. Those who wish to examine the evidence *pro* may read Dr Wiltie's book with profit.

M C P

The Human Body By LOGAN CLENDENING, M D 443 pages, 16 X 24 cm Alfred
A Knopf, New York 1937 Price, \$3.75

Dr Clendenning, in the letter to Dr P T Bohan, which forms the preface and dedication of this book, states that it was written "to make intelligible some of the intricacies of the human body for the adult and otherwise sophisticated reader." Actually, he has produced an outline of human biology, physiology, anatomy, and pathology, flavored throughout by his vigorous, sometimes acid, but always interesting personal philosophy.

The work is divided into four sections titled: The Human Body as a Unit, The Human Body as an Organism for the Conversion of Food and Air into Energy and into Tissue, The Human Body as an Organism for the Reproduction of Its Own Kind, and The Human Body and Disease. Each section, as may be surmised, takes up a different aspect of the relation of the body to itself and its environment.

Those who are familiar with Dr Clendenning's virile style and acquainted with the worth of his medical writing, need not be told that he is an ideal author for a popular work of this type. It fulfills all expectations, and is fully recommended.

T N C

COLLEGE NEWS NOTES

ANNUAL MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

New Orleans, La , March 27-31, 1939

The 1939 meeting of the American College of Physicians will be held in New Orleans at a particularly delightful time of the year. The weather is usually warm, the sun shines brightly and all the spring flowers are out in all their glory. The New Orleans members of the College are looking forward with a great deal of pleasure to welcoming the Fellows throughout the country at this annual convocation.

The Executive Committee and the Sub-Committees consist of the following Fellows

General Sessions and Lectures

William J Kerr, President

General Chairman

J H Musser

Committee on Arrangements

P H Jones
Allan Eustis
Edgar Hull

Robert Bernhard
John Lanford
Randolph Lyons

Committee on Clinics and Demonstrations

P H Jones, Chairman

O W Bethea
J M Perrett

W L Smith
C S Holbrook

W R Wirth

Committee on Transportation

Edgar Hull, Chairman

L A Monte

R H Bayley

G R Williamson

Committee on Entertainment

Robert Bernhard, Chairman

Anees Mogabgab
D N Silverman

Ben Heninger
Grace Goldsmith

Committee on Auditorium

Allan C Eustis, Chairman

C Tripoli

G M Decherd

Committee on Publicity

John Lanford, Chairman

M E Bass
C J BloomClyde Brooks
Maud Loeber

C W Duval

Committee on Round Tables

Randolph Lyons Chairman

C C Bass

J M Bamber

J C Cole

Ladies Entertainment Committee

Mrs C Grenes Cole, Chairman

The Executive Committee and its subdivisions are arranging for the round table conferences, the clinics at the hospitals and the entertainment for the visiting members. To speak of the last first, it might be said that the Smoke will be held on Monday evening. It will be held at the Roosevelt Hotel, which will be the headquarters for the meeting. On Tuesday night there will probably not be any session, but the opportunity will be given to the Fellows of enjoying the pleasures and hospitality of the city. Wednesday night the Convocation will be held at the Hotel Jung, which is designated as Convocation hotel, and will be followed by the President's Reception. On Thursday night will be held the annual Banquet, at which it is hoped to have two of the literary lights of New Orleans address the diners.

The arrangements of the meetings will be different than they were last year in New York. On Tuesday and Thursday mornings from 9 00 to 11 00 dry clinics will be held in the Auditorium. On the same days from 10 00 to 12 00 will be held round table conferences. The dry clinics will be held in part by the local men and in part by invited guests. For the round tables so far the following speakers have promised to conduct these meetings: in cardiology, Dr Fred M Smith, F A C P, Iowa City, nutrition, Dr James McLester, F A C P, Birmingham, blood dyscrasias, Dr Roy R Kracke, Emory University, Ga, radiology, Dr B R Kirklín, F A C P, Rochester, Minn, bacterial chemotherapy, Dr P H Long, Baltimore, gastro-enterology, Dr Lay Martin, F A C P, Baltimore, nephritis, Dr William S McCann, F A C P, Rochester, N Y. In addition to these speakers, it is planned to have an outstanding surgeon conduct a round table conference on medico-surgical problems. The infectious diseases will also be considered, a pediatrician has been invited and a psychiatrist. There will also be held a round table conference on the animal parasitic diseases. There will be a sufficient number of leaders in these conferences to ensure relatively small groups, so that personal contacts between speaker and audience may be maintained. On Wednesday and Friday mornings there will be hospital clinics held at the Charity Hospital, Touro Infirmary, Baptist Hospital and possibly one of the other hospitals. The Charity Hospital's new building will not be completed, but the clinics will be held in the adjoining medical school building of Louisiana State University. Because of the limitation in hospital accommodations, on these same mornings from 10 00 to 12 00 lectures will be delivered at the Auditorium. It will be noted there is some overlapping of the hours. This has been done deliberately, in order to permit a greater selection of special features than otherwise would be possible.

The General Sessions will be from 2 00 to 5 00 in the afternoon and Monday night from 8 00 to 10 00. The headquarters hotel will be the Roosevelt Hotel, and, if the Fellows wish to stay in this hotel, reservations should be made promptly, as already the greater part of the hotel has been filled. The convocation hotel will be the Jung Hotel. This hotel is a splendid caravansary. The room in which the Convocation will be held has just been constructed and is a truly beautiful room. There are many other good hotels in New Orleans, practically all of them centrally located only a few blocks from the Auditorium and Charity Hospital, but it is urged that the Fellows make their reservations as early as possible, as there are a large number of tourists in New Orleans at this time of year and sometimes it is difficult to secure accommodations.

Mrs C Grenes Cole, wife of Dr Cole, who is a former president of the Orleans Parish Medical Society, and at present president of the Woman's Auxiliary of the Society, has arranged for a series of delightful entertainments for the women visitors. These will include trips through the old French Quarter with guides, river rides, luncheons, teas, trips to some of the old plantation homes and other entertainments which will keep the wives and feminine members of the family of the members busy during the scientific sessions.

President Kerr reports that an excellent program of General Sessions and special lectures is being arranged, which will present important recent and new contributions from the clinical sciences, the practice of medicine, including titles from the fields of pediatrics, neuropsychiatry, dermatology and syphilology, and surgery. The speakers are being chosen with great care, not only for their subjects but also for their ability to present them well. Officers, Regents and Governors of the College, as well as medical schools and hospitals, have been canvassed by President Kerr, and he has received a fine response concerning available subjects and the desires of those who know the needs.

POSTGRADUATE COURSES

In further pursuance of the policy of organizing and offering special limited postgraduate courses especially for members of the College and those preparing either to meet the requirements for certification by the American Board of Internal Medicine or the requirements for Fellowship in the College, the American College of Physicians will conduct such a series of courses during the two weeks, March 13 to 25, inclusive, 1939, preceding the Annual Session of the College. At a meeting of the Committee on Postgraduate Courses, consisting of Dr Hugh J Morgan, F A C P, Chairman, Nashville, Tenn, Dr Charles Sidney Burwell, F A C P, Boston, Mass, Dr Joseph A Capps, F A C P, Chicago, Ill, Dr Charles H Cocke, F A C P, Asheville, N C, Dr William J Kerr, F A C P, San Francisco, Calif, and Mr E R Loveland, Executive Secretary of the College, at New York City on October 16 the following tentative outline of courses was determined upon:

- A Baltimore, Md (under chairmanship of Dr M C Pincoffs, F A C P), Johns Hopkins University School of Medicine and the University of Maryland School of Medicine cooperating
 - 1 General Medicine
 - 2 Cardio-Respiratory Diseases
- B Chicago, Ill (under chairmanship of Dr James G Carr, F A C P)
 - 3 General Medicine, University of Illinois College of Medicine
 - 4 Cardiology, Northwestern University Medical School
 - 5 Research Review, University of Chicago Clinics
- C St Louis, Mo (under chairmanship of Dr David P Barr, F A C P)
 - Washington University School of Medicine

- 6 Cardiology
- 7 Internal Secretions
- 8 Dermatology and Allergy in Relation to Internal Medicine
- D Nashville, Tenn (under chairmanship of Dr John B Youmans, F A C P)
Vanderbilt University School of Medicine
- 9 General Medicine

The response to the program conducted last year in Boston, New York and Philadelphia, was so gratifying that this activity is being extended. Keen interest has been indicated in other special courses, but inasmuch as the program is still in its experimental stage, the Committee has determined not to overexpand the number of courses given. These courses will be made available at minimum cost, because the College itself will assume full responsibility for promotion, advertising, printing and registration, as its contribution to its members. It is anticipated that the registration fee for each course will be \$40 00, and that the detailed bulletin of the courses will be ready for distribution by January 1.

THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

Dr Noble Wiley Jones, F A C P , Portland, Ore , Second Vice President, will be the official representative of the American College of Physicians at the Inauguration of the Royal Australasian College of Physicians, to be held in Sydney Australia, December 15, 1938. This body has been formed among the physicians of Australia and New Zealand. Dr Allan S Walker, 185 Macquarie St, Sydney, Australia, is the Honorary Secretary.

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Reprints

- Dr L Minor Blackford (Associate), Atlanta, Ga —four reprints,
- Dr Ralph O Clock, F A C P , Scarsdale, N Y —one reprint,
- Dr Perk Lee Davis (Associate), Philadelphia, Pa —three reprints,
- Dr Lorenz W Frank, F A C P , Denver, Colo —four reprints,
- Dr Paul J Hanzlik, F A C P , San Francisco, Calif —twenty-eight reprints,
- Dr M Coleman Harris, F A C P , New York, N Y —one journal,
- Dr Jerome George Kaufman (Associate), Newark, N J —two reprints,
- Dr Oliver M Layton, F A C P , Fond Du Lac, Wis —one reprint,
- Dr James B McLester (Associate), Birmingham, Ala —four reprints,
- Dr F M Pottenger, F A C P , Monrovia, Calif —one reprint,
- Dr Willard C Rappleye, F A C P , New York, N Y —one reprint,
- Dr William B Rawls, F A C P , New York N Y —one reprint

FROM THE COLLEGE ARCHIVES

The most valuable addition to the Archives of the College obtained recently is a copy of the "Transactions of the American Congress on Internal Medicine, 1917," donated to the College Library by Dr Clement R Jones, F A C P , Pittsburgh, Pa , former Treasurer of the College. The "Transactions" were published in book form, and give early details concerning the "Second Scientific Session" conducted under the auspices of the American Congress on Internal Medicine, which was the affiliated

society conducting the annual programs and acting as a feeder to College membership. The Pittsburgh proceedings disclose many of the early problems in the organization of the American College of Physicians, and in a published obituary it is disclosed that Dr. Heinrich Stern, the first Secretary General of the College, was the chief motivating spirit behind the formation of both the American Congress on Internal Medicine and the American College of Physicians. Quoting therefrom, "Dr. Stern conceived the idea of a congress of internists, that should not be limited to those in prominent teaching positions but that should be open to all of the profession who were particularly interested in internal medicine—and among those, who by meritorious work, study and investigation had done something for the good of humanity and the profession, a certificate, *causa honoris*, in the American College of Physicians, should be given. These dreams and ideals he repeated time and again to his friends until finally he interested some of his professional brethren who saw the truth and possibilities of his concept. After much labor and deliberation, stimulated and abetted by his enthusiasm, the American Congress on Internal Medicine and its exemplar—the American College of Physicians—were formed. When these were fully organized and had justified his prophecy, it was denied him, as it was to Moses of old, that he should see the promised land in the progress and brilliant success of these organizations which will be permanent memorials of their founder and the ideals of the internists and consultants which have become actualities."

SECTIONAL WEST VIRGINIA MEETING, AMERICAN COLLEGE OF PHYSICIANS

A joint meeting of the West Virginia members of the American College of Physicians and the West Virginia Heart Association and the Cabell County Medical Society was held at Huntington, W. Va., October 13, 1938. Dr. Oscar B. Biern, F.A.C.P., Huntington, and Dr. P. A. Tuckwiller (Associate), Charleston, are President and Secretary, respectively, of the West Virginia group of the College. Dr. Tuckwiller is also Secretary of the West Virginia Heart Association and Dr. R. J. Condry, F.A.C.P., Elkins, is President. The program was as follows:

10:30-12:00 St. Mary's Hospital

DEMONSTRATION OF HEART CASES

Technic of Lateral Fluoroscopy, Lateral Chest Plates, etc.)

Dr. Sam Brown, Cincinnati, Ohio; Dr. A. Carlton Ernstene, Cleveland, Ohio; Dr. Julien Benjamin, F.A.C.P., Cincinnati, Ohio

2:00 p.m. Ball Room Hotel Governor Cabell

ROENTGENOLOGICAL DIAGNOSIS OF HEART DISEASE

Dr. Sam Brown, Cincinnati, Ohio

3:00 p.m. Ball Room Hotel Governor Cabell

COMMON ERRORS IN CARDIAC DIAGNOSIS

Dr. A. Carlton Ernstene, Cleveland, Ohio

4:00 p.m. Ball Room Hotel Governor Cabell

ELECTROCARDIOGRAPHIC SLIDES DEMONSTRATION

Dr. Julien Benjamin, F.A.C.P., Cincinnati, Ohio

6:30 p.m. Dinner—Hotel Governor Cabell

8:30 p.m. Ball Room Hotel Governor Cabell

Joint meeting of the West Virginia Heart Association, West Virginia Branch of the American College of Physicians and the Cabell County Medical Society

SURGERY OF THE HEART

(With motion pictures and lantern slide demonstration)

Dr. Calude S. Beck, Professor of Surgery, Western Reserve University, Cleveland, Ohio

The College of Physicians of Philadelphia has instituted a program of semi-public lectures to the laity during the coming winter. Dr Alfred Stengel, M A C P, on November 18 will deliver one of these addresses on "Currents and Counter-Currents in the Progress of Medicine"

Dr E J G Beardsley, F A C P, Philadelphia, was the guest speaker at the initial autumnal meeting of the Hudson County (N J) Medical Society at Jersey City, on October 4. A clinical conference was held at the Medical Centre, Jersey City.

Dr Beardsley also addressed the Burlington County (N J) Medical Society on October 13 at the first meeting of the autumn, which was held at the Moorestown Country Club, Moorestown, N J, on "Routine and Systematic Physical Examinations versus Intuitive Diagnoses"

Dr J Merriman Lynch (Associate), formerly of Panama City, is now engaged in practice in Pasadena, Calif, limiting his work to Internal Medicine and Tropical Diseases. He was recently appointed Instructor in the University of Southern California School of Medicine.

In tribute and appreciation to Dr F M Pottenger, F A C P, Monrovia, Calif, there has grown a custom of an annual home-coming of ex-patients at the Pottenger Sanatorium. More than two hundred patients, former patients and friends foregathered at the Sanatorium on September 25. Representatives were present from the various years since the establishment of the Sanatorium in 1903, including one ex-patient who was at the Sanatorium twenty-five years ago. It is the custom of the Sanatorium to keep in touch with all former patients. Contact is still maintained with eleven of the thirty-six patients who were treated at the Sanatorium in 1904, one year after its founding. Since establishment of the Sanatorium, more than 12,000 patients have been treated there. When the Sanatorium was opened in 1903, the death rate from tuberculosis was about 200 per 100,000 population. Today it is approximately 53 per 100,000 population. In Dr Pottenger's address at the foregathering, he predicted that because of the progress in treatment and education, the death rate from tuberculosis may be further reduced in the next decade to 20 per 100,000 population.

Dr August A Werner, F A C P, St Louis, addressed the Mississippi Valley Medical Society at Hannibal, Mo, September 30, on the subject of the anterior-pituitary gonad relationship in the female.

Dr Lowell D Snorf, F A C P, Assistant Professor of Medicine at Northwestern University Medical School, Chicago, addressed the ninety-fourth annual meeting of the Northwestern Ohio Medical Association October 4 on "Functional Disorders of the Intestinal Tract"

Dr George W McCoy, F A C P, Surgeon, U S Public Health Service, is now on duty in New Orleans as head of the Department of Preventive Medicine and Public Health, Louisiana State University Medical Center.

Dr A C Woofter (Associate), Parkersburg, W Va, has been appointed physician in charge of the health department of the Parkersburg city-county schools.

Dr Horace K Richardson, F A C P, Assistant Medical Director of The Austen Riggs Foundation, Stockbridge, Mass, gave the annual Mental Hygiene Lecture at Vassar College on October 10, 1938

Dr Walter F Donaldson, F A C P, Secretary, has announced that the eighty-ninth annual session of the Medical Society of the State of Pennsylvania will be held in Pittsburgh, October 2-5, 1939

Dr Frank L Jennings, F A C P, for a number of years Associate Medical Director of the Glen Lake Sanatorium, Oak Terrace, Minn, and Instructor in Medicine, University of Minnesota Medical School, Minneapolis, has been named Superintendent of the Marion County (Ind) Tuberculosis Hospital at Sunnyside. He succeeds Dr A E Hubbard, who died September 15. Dr Jennings is a graduate of Syracuse University College of Medicine and is a past president of the Mississippi Valley Sanitarium Association. For three years he was assistant physician at the New York State Sanitarium at Raybrook, N Y, having gone to the Glen Lake Sanatorium in 1917. This institution has been enlarged from a 50-bed capacity, when Dr Jennings first was associated with it, to one of 700 beds.

The Liaison Committee and the Committee on Postgraduate Education of the American College of Physicians were invited to confer with like committees of the American College of Surgeons at the latter's annual session in New York City, beginning October 17. The delegates from the American College of Physicians were also invited to attend the 21st Annual Hospital Standardization Conference. The committees will make a survey and report to the Board of Regents on any matters of mutual interest and possible cooperation between the two Colleges.

The 49th annual convention of the Association of Life Insurance Medical Directors of America was held in Philadelphia October 20-21, under the presidency of Dr Samuel B Scholz, Jr, F A C P, Medical Director of the Penn Mutual Life Insurance Company of Philadelphia. Every life insurance company with home offices in the United States or Canada was invited to participate in the discussions. Dr Harry E Ungerleider (Associate), Assistant Medical Director of the Equitable Life Assurance Society, New York, N Y, presented a paper on "A Study of the Transverse Diameter of the Heart Silhouette With Prediction Table Based on the Teleoroentgenogram" and Dr J Hamilton Crawford, F A C P, Professor of Clinical Medicine at Long Island College of Medicine, and Dr C E de la Chapelle, F A C P, Assistant Professor of Medicine, New York University College of Medicine, led the discussion.

The Sixteenth Annual Scientific Session of the Academy of Physical Medicine was held in Washington, D C, October 24-26, 1938. Among members of the College contributing were the following:

- Dr William A Swalm, F A C P, Philadelphia, "Gastrosopic Control in the Treatment of Diseases of the Stomach",
- Dr Frank H Krusen, F A C P, Rochester, Minn, "Biological Aspects of Light Therapy"

The Sixth Annual Assembly of the Omaha Mid-West Clinical Society was held October 24-28, under the Presidency of Dr. Bryan M. Riley, F A C P. The following members of the College participated in the program:

- Dr. Henry L. Bockus, F A C P, Philadelphia, leader of a round table on "The So-Called Irritable Colon," a formal paper on "Practical Application of Recent Advances in Our Knowledge of Liver Function," a formal paper on "Diagnosis and Treatment of Chronic Gastritis" and a clinic on "Gastro-intestinal and Hepatic Disorders",
- Dr. O. H. Perry Pepper, F A C P, Philadelphia, Pa., leader of a round table on "The Importance of Hypotension," formal papers on "Principles of Diagnosis and Treatment of Diseases in the Elderly" and "Recognition and Treatment of Anemia Due to Increased Blood Destruction" and a clinic on "Hematology",
- Dr. John F. Gardiner, F A C P, Omaha, radio broadcast, "Overweight",
- Dr. G. A. Young (Associate), Omaha, scientific exhibit on "Convulsions—Their Treatment and Therapeutic Use in Psychoses",
- Dr. A. F. Tyler, F A C P, Omaha, scientific exhibit (motion picture in color), "Radiation Therapy",
- Dr. F. Lowell Dunn, F A C P, Omaha, scientific exhibit, "Arthritis",
- Dr. E. L. MacQuiddy (Associate), Omaha, scientific exhibit, "Lung Changes Produced by Chronic Nitric Oxide Inhalation and by Dust Inhalation",
- Dr. Chester Thompson (Associate), Omaha, a lecture on "Errors in Cardiac Diagnosis",
- Dr. M. W. Barry, F A C P, Omaha, a lecture on "Treatment of Cardiovascular Syphilis",
- Dr. H. A. Wigton, F A C P, Omaha, a lecture on "Encephalitis—Types and Treatment",
- Dr. Ernest Kelley, F A C P, Omaha, a lecture on "The Use of Metrazol in Mental Diseases",
- Dr. John F. Gardiner, F A C P, Omaha, a lecture on "The Knowledge Required of the General Practitioner in the Present Day Treatment of Pulmonary Tuberculosis",
- Dr. John R. Kleyla, F A C P, Omaha, a lecture on "Broncho-Sinusitis".

Dr. Lauren H. Smith, F A C P, Associate in Psychiatry, University of Pennsylvania School of Medicine, and Executive Medical Officer, Institute of the Pennsylvania Hospital, has recently succeeded Dr. Earl D. Bond as Physician-in-Chief and Administrator of the Pennsylvania Hospital's Department of Mental and Nervous Diseases and as Director of the Institute.

Dr. N. S. Davis, III, F A C P, Chicago, is President of the Chicago Academy of Sciences, having formerly acted as Secretary. During June, 1938, Dr. Davis was also made President-Elect of the Chicago Medical Society. On November 3, 1938, Dr. Davis discussed "Treatment of Arteriosclerotic Heart Disease" before the Southern Illinois Medical Association at East St. Louis, Ill., and on November 15 he presided at a clinical conference at a special meeting of the Fellows and Associates of the College of Southern Illinois. This sectional meeting of the College was held at Decatur, under the chairmanship of Dr. Samuel Munson, F A C P, Governor of the College for Southern Illinois.

OBITUARY

DR LESTER I LEVYN

Lester I Levyn (Fellow, A C P, 1922) died at his home in Buffalo, N Y, on June 24, 1938, after an illness of three years. He was a life-long resident of Buffalo, having been born there on December 28, 1887. He was graduated from the University of Maryland Medical School in 1909.

Following his graduation he went into the general practice of medicine for a few years. He then went abroad for the study of roentgenology, especially in the Berlin and London clinics. He followed this with some postgraduate work at the Harvard University Medical School. On his return he limited himself to the practice of roentgenology, which he continued to the time of his death.

He was a member of the following societies: The Buffalo Radiological Society, The Buffalo Academy of Medicine, The Erie County and New York State Medical Societies, The American Medical Association, The American Roentgen Ray Society and the Radiological Society of North America. He became a Fellow of the American College of Physicians in 1922.

Dr Levyn carried on an extensive private practice and in addition was, for many years, director of the Department of Roentgenology of the Deaconess Hospital. His illness, leukemia, forced him to relinquish this post about two years ago. During his career he made many contributions to the roentgenological literature. He was particularly interested in cholecystography and published many articles pertaining to it.

Early in 1935 he learned of the fatal nature of his last illness. In spite of this knowledge he carried on his practice and hospital work with the same skill and efficiency as ever. To his intimates and associates, who knew of his affliction, his fortitude and courage were the subject of great admiration. Within the last year he continued his publications, preparing and delivering a paper at the International Congress of Radiology.

In addition to his professional interests, Dr Levyn was active in many local enterprises. He was particularly interested in sectarian charitable institutions and served on many boards up to the time of his death.

He was unmarried and is survived by a sister and brother. In his death, both the profession and the community have lost a valuable and stimulating member.

NORMAN HEILBRUN, M D

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HEART FAILURE OR ACUTE NEPHRITIS WITH ONSET ABOUT THREE WEEKS AFTER DELIVERY *

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THE vast literature of the abnormal puerperium concerns itself almost entirely with complications immediately preceding labor, during labor, and in the first ten days postpartum. Those complications manifested later, especially with an interval of apparent health before their development, have received but little consideration. A group of cases representing such puerperal complications has been seen in the Tulane medical unit of the Charity Hospital of Louisiana. At least two distinct groups have been recognized, (1) patients without evidence of disease until the puerperal period, who, within three to five days following delivery, developed signs of sepsis, followed in 14 to 21 days by the appearance of acute, diffuse hemorrhagic nephritis, and (2) those patients who, 14 to 25 days postpartal, developed frank congestive heart failure in spite of the fact that during pregnancy and labor there had been no definite evidence of heart disease. Search of the obstetrical and medical literature reveals that these clinical pictures are not well known, and that they have been inadequately and unsystematically described. This paper is an attempt not only to establish a tentative classification of these syndromes but also to discuss the probable mechanisms of symptom production as they are peculiarly related to the puerperal state, and to emphasize the relationship between pregnancy and these symptoms.

These types are illustrated by the following case reports

CASE REPORTS

Case 1 J D, married negress, aged 38, entered the Charity Hospital October 1, 1933, complaining of edema of the face and lower extremities. Her health in the past had been generally good. There was no history of soreness of the throat nor of scarlet fever. She had been pregnant six times. All pregnancies went to full term except the fifth which resulted in miscarriage at four months. She applied

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to the obstetrical out-patient department in the early months of the last pregnancy. No signs of toxemia were ever noted. On August 7, 1933, she complained of constipation and slight swelling of the feet. Blood pressure was then 106 mm of mercury systolic and 70 diastolic. Urinalysis showed no albumin, sugar, casts nor red blood cells. On September 2, 1933, the urinalysis was again unchanged. She came to the hospital in labor on September 6, 1933, and delivered spontaneously a full term child. No untoward symptoms developed until the second day postpartum when she experienced chills and fever, symptoms which remained for five days in varying degree, the temperature reaching 103° F. The lochia appeared normal. The temperature then returned to normal and the patient was discharged on the fourteenth day. Urinalysis had disclosed no cause for the fever. The patient then led a restricted life with freedom from symptoms until the tenth day at home when she awakened in the morning and noted a puffiness about the eyes and edema of the feet and hands. Severe frontal headaches developed. The urine became red and reduced in amount for three days. Palpitation for three to four minute intervals was noted at times and dyspnea occurred on exertion. A dry cough ensued. There were no dizziness, spots before the eyes, nor sore throat. Because the symptoms failed to subside she applied for admission to the hospital.

Examination on admission disclosed a well developed and well nourished negress of sthenic habitus, lying quietly in bed. The height was 65 inches, weight 120 pounds, blood pressure 160 systolic and 90 diastolic, respiration 20 per minute, pulse 86 per minute, temperature 98.6° F. She did not appear acutely ill. A distinct puffiness was noted about the eyes. The pupils reacted to light and accommodation. The conjunctivae were pale. Oral hygiene was good. There were many gold fillings. The chest was symmetrical. The lungs were clear to physical examination. The heart was not demonstrably enlarged, P.M.I. was in the fifth interspace 7½ cm from the midsternal line. The left border of cardiac dullness was 0.5 cm further to the left. P₂ was less than A₂. There were no murmurs. The breasts were lactating. The abdomen showed slight distasis recti. The lower border of the liver was barely palpable. Some deep tenderness below the right costal margin was elicited. No rigidity or muscle spasm was found. Pelvic examination disclosed a foul purulent discharge. The cervix was bilaterally lacerated. The fundus was felt anteriorly and showed subinvolution. No adnexal masses were felt. The extremities displayed a tense glistening skin with pitting edema below the knees. Venous pressure was not demonstrably elevated with hand placed upon the thigh.

Laboratory Work On admission the blood findings were red blood cells 3,270,000, white blood cells 9,500, hemoglobin 75 per cent, non-protein nitrogen 29, urea nitrogen 15, sugar 102 mg per cent, Wassermann negative. The urine showed specific gravity 1.012 to 1.014, albumin 14 per cent (wet), sugar negative, many hyaline, fine and coarse granular casts, six to eight red blood cells per high power field, numerous white blood cells per high power field. The phenolsulphonephthalein output was 30 per cent in two hours. The serum proteins on September 11, 1933, were albumin 2.43, globulin 1.94, total 4.37 gm per cent. Cystoscopic examination disclosed findings similar to those recorded above with no growth in cultures. Cervical cultures were negative for streptococci.

On discharge from the hospital on October 21, 1933, the urine still showed red blood cells, casts and albumin (7.8 per cent). The edema had entirely cleared and symptomatically the patient was relieved. The blood pressure was then 155 systolic and 90 diastolic. The patient returned home to an outlying parish to continue treatment with her local physician.

Case 2 A M., married negress, aged 20, entered the hospital on March 22, 1933. She had not menstruated since January 1933, and complained of nausea and vomiting which were easily controlled. Physical examination at that time was not remarkable except for a three months pregnancy. There were no previous preg-

nancies Laboratory data at that time disclosed the following Urine showed a specific gravity of 1.024, albumin plus, sugar negative, no casts, no red blood cells, 10 white blood cells per high power field The phenolsulphonephthalein output was 80 per cent in two hours, non-protein nitrogen 26 to 28, blood sugar 95 mg per cent, red blood cells 4,395,000, white blood cells 6,000, hemoglobin 80 per cent

She was not seen again until September 7, 1933, when she entered the hospital complaining of cramp-like abdominal pains and vaginal bleeding The uterus was enlarged above the umbilicus and was contracting at intervals On September 8, 1933, she aborted There was little postpartal bleeding The urine was negative for albumin, casts and red blood cells The blood pressure was 130 systolic and 80 diastolic The temperature, which was 103° F on admission, dropped to normal on the third day On the tenth day she was discharged

She again applied for admission on November 28, 1933, complaining of dyspnea and pain in the right side of the chest She stated that two weeks following her miscarriage she developed edema of the ankles Her face appeared somewhat swollen Urine became reduced in amount but was not discolored There was no dyspnea, dizziness, nor spots before the eyes Ankle edema continued, improving at times, but gradually becoming more severe and, for two weeks before admission, was accompanied by progressive dyspnea There was no past history of sore throats nor scarlet fever

Examination on admission disclosed a young negress lying propped up on the bed appearing seriously ill and obviously anemic The face was edematous Pupils reacted to light and accommodation No exudate was seen in the fundi Oral hygiene was good The tonsils were not inflamed The thyroid was bilaterally symmetrically enlarged The lungs showed no evidence of congestion The heart was enlarged to the left, the apex beat being one centimeter to the left of the midclavicular line in the fifth interspace The rate was 100 per minute The rhythm was regular No murmurs were heard but a protodiastolic gallop rhythm was heard at the apex The blood pressure was 144 systolic and 116 diastolic The abdomen showed a fluid wave and shifting dullness The liver was not felt The legs and thighs showed marked pitting edema Pelvic examination disclosed a bilaterally lacerated cervix

Laboratory Work The urine was acid, specific gravity 1.016, albumin ++++, occasional white blood cells, 10 to 15 red blood cells per high power field, many coarse and fine granular casts An Addis count on January 6, 1934, disclosed casts 684,000, red blood cells 24,320,000, epithelial and white blood cells 56,130,000 An examination of the blood showed 2,700,000 red blood cells, 9,400 white blood cells, hemoglobin 50 per cent The phenolsulphonephthalein was 40 per cent in two hours The non-protein nitrogen was 28, urea nitrogen 13, creatinine 1.0, sugar 83 mg per cent The Wassermann was strongly positive The serum proteins were albumin 1.90, globulin 2.59, total 4.49 gm per cent The electrocardiogram showed T₁ inverted and a sinus tachycardia The teleoroentgenogram showed the transverse diameter of the chest to be 27 cm, the transverse diameter of the heart 17.3 cm The basal metabolic rate was +2 per cent

The patient improved symptomatically and, on December 23, 1933 signed her own discharge On January 1, 1934, eight days later, she was readmitted with edema more marked than before Besides the marked generalized edema and ascites, there was a bilateral hydrothorax The blood pressure was 165 systolic and 120 diastolic Small areas of exudation were seen in the macular region on fundus examination The non-protein nitrogen rose to 52 mg per cent, urea nitrogen to 27 The urine was essentially unchanged The phenolsulphonephthalein was 15 per cent in two hours The patient went into coma and died in two days No autopsy was obtained

Case 3 P. W., negress, aged 22, entered the Charity Hospital on October 5, 1933, complaining of headache and swelling of the face and ankles In the past she

had been well. She had had a sore throat in 1930. There was no history of scarlet fever nor of joint pains. She became pregnant for the first time in January 1933, and attended the obstetrical clinic for antepartum care. No significant symptoms arose during this period. Blood pressure varied from 120 systolic and 82 diastolic to 118 systolic and 78 diastolic. The urine was repeatedly negative for albumin, sugar, red blood cells and casts. No edema nor headache developed. On September 10, 1937, she delivered spontaneously a 7½ pound child which lived 15 days. Blood pressure during labor rose to 144 systolic and 88 diastolic. On the third day postpartum she began to have fever which lasted three days and reached 103° F. A chill accompanied the onset of fever. The urine appeared dark brown for several days following the chills and fever, and burned on passage. Pus cells only were found at this time. She was discharged on September 21, 1933. Several days later she noticed for the first time swelling of her face, especially about the eyes, and also of the legs. Severe frontal and parietal headache developed with slight vertigo and spots before the eyes. She became nauseated but did not vomit. Symptoms became progressively worse. Headache became so severe that she walked the floor at night and cried out in pain. Her neck felt stiff.

Examination on admission disclosed an hypersthenic young negress lying very restlessly in bed, holding her head in her hands and obviously in great pain. The facies was anxious. The height was 65 inches, weight 130 pounds, blood pressure 175 systolic and 125 diastolic, respiration 22 per minute, pulse 100 per minute, temperature 99° F. The face was markedly edematous, the eyes almost closed with the edema. Pupils reacted to light and accommodation. Mucous membranes were pale. The tonsils were not inflamed. The breasts were lactating. The lungs were not remarkable. Heart. Point of maximum impulse was found 10 cm from the mid-sternal line in the fifth interspace, the left border of cardiac dullness 10.5 cm from the midsternal line in the fifth interspace. A harsh blowing systolic murmur was heard along the left border of the sternum. P_2 was greater than A_2 , and both were accentuated. In the abdomen no signs of fluid were elicited. The liver and spleen were not felt. Pelvic examination disclosed subinvolution and retrodisplacement of the uterus. The cervix was soft. The extremities displayed moderate pitting edema in the lower half of both legs.

Laboratory Work. On admission the urine was acid, the specific gravity 1.018, albumin ++, sugar negative. A few red blood cells and fine granular casts were found. An Addis count on October 28, 1933, disclosed a volume of 300 c.c., red blood cells 156,000,000, casts 750,000, pus and epithelial cells 75,000,000. Non-protein nitrogen was 28, blood sugar 88 mg per cent. Blood Wassermann was negative. Serum proteins on October 8, 1933, were albumin 3.13, globulin 2.34, total 5.47 gm per cent. The teleoroentgenogram showed the transverse diameter of the chest to be 25 cm, transverse diameter of the heart 13.5. Spinal fluid examination showed a pressure of 10 mm of mercury, less than 10 cells per cubic millimeter, Wassermann negative, no red blood cells and a negative globulin reaction.

The edema rapidly disappeared with treatment. The urinary protein diminished markedly and the hematuria became very slight. Blood pressure fell only to 170 systolic and 115 diastolic. On November 2, 1933, the patient was discharged to her local physician for treatment at home.

Case 4. V. S., 16 year old negress, gave a history similar to that of Case 3 except for a forceps delivery. On the nineteenth day postpartum she suddenly developed headache and dizziness. Edema of the eyes and ankles developed on the twenty-fourth day postpartum and lasted one day only. The next day headache became more severe, blurring of vision ensued, and she suddenly had a generalized convulsion, which prompted admission on November 11, 1933. She had had occasional sore throats when a child.

Examination disclosed evidence of the convulsion in a beefy, bleeding tongue

There was moderate edema of the face and legs. The ocular fundi were negative except for narrowed arteries. The breasts were lactating. The heart and lungs were not remarkable. The blood pressure was 158 systolic and 104 diastolic. Pelvic examination disclosed a subinvolted uterus.

Laboratory Work Spinal fluid pressure was 14 mm of mercury, cells less than 10, globulin, Wassermann and gum mastic negative. Blood chemistry disclosed non-protein nitrogen 27, blood sugar 70 mg per cent. Urine showed a specific gravity of 1.020, acid, albumin ++++, many red blood cells and coarse granular casts on three examinations (catheterized). Phenolsulphonephthalein was 45 per cent in two hours.

She had two convulsions after admission and then symptoms receded. By November 15, 1933, date of discharge, she was symptom free. The edema and urinary findings had disappeared and the blood pressure was 140 systolic and 70 diastolic.

Case 5 D H, 25 year old negress, entered the Charity Hospital on October 9, 1933, and delivered a full term child the next day by forceps delivery. There was no evidence of renal disease at that time. The blood pressure was not elevated. The postpartal stay in the hospital was uneventful except for a rise of temperature to 101° F on the fourth and fifth days. About 16 days postpartum she experienced a severe headache, and her vision blurred at times. She felt feverish but did not take her temperature. Edema made its appearance about the face and ankles. Symptoms continued and on November 9, 1933, 29 days after delivery, generalized twitching movements unaccompanied by loss of consciousness prompted admission to the hospital. In the past there was no history of rheumatic fever, scarlet fever, nor acute tonsillitis. She had been pregnant five times before, resulting in four miscarriages and one full term living child.

Examination disclosed generalized edema, especially noticeable over the eyelids. The blood pressure was 156 systolic and 100 diastolic, temperature 98° F, pulse 90 per minute. The retinal vessels appeared normal. The tonsils were enlarged but not acutely inflamed. The lungs showed some fine basal râles posteriorly. The heart was not demonstrably enlarged to the left. An apical systolic murmur, untransmitted, was heard. P_2 was greater than A_2 . The abdomen showed no evidence of ascites. Pelvic examination was not done.

Laboratory Work Examination of the urine showed a specific gravity of 1.016, cloudy, acid, albumin ++++, many red blood cells, white blood cells and coarse granular casts. The non-protein nitrogen was 30, blood sugar 97 mg per cent and the Wassermann test weakly positive.

The patient became progressively worse. Dyspnea became more marked, basal râles increased until there was marked pulmonary edema. The blood pressure remained in the range of 168 systolic, 115 diastolic to 152 systolic and 92 diastolic. The pulse became thready and the patient died in acute heart failure. No autopsy could be obtained.

Case 6 A T, married negress, aged 20, entered the Charity Hospital on February 27, 1934, complaining of swelling of the legs. In the past she had always been well. She had measles and mumps as a child but no sore throats, scarlet fever nor anything which might be construed as a streptococcal infection. There was no history of hematuria nor other urinary symptoms. The family history was irrelevant. She had had her first child two years before. At that time there was no edema, no urinary nor cardiac symptoms. Delivery was uneventful. She was well, then, until January 5, 1934, when she entered the obstetrical ward of Charity Hospital. For several days she had noted a slight swelling of the ankles which disappeared on lying down. The history at that time revealed no headache, vertigo, epistaxis, nausea nor urinary symptoms. There were no symptoms nor signs of eclampsia. Blood pressure was 122 systolic and 80 diastolic. Urine on three occasions showed no albumin, casts, nor red blood cells. On January 12, 1934, she delivered spontaneously. On

the first day postpartum the temperature rose suddenly to 101° F and remained irregularly elevated until January 19, 1934, when it returned to and remained normal following the use of urinary antiseptics given because of the presence of white blood cells in the urine. She was discharged on January 21, 1934, and felt perfectly well for 14 days, when her ankles began to swell. No dyspnea nor vertigo developed. The urine became reduced in amount but no hematuria was noted. The edema became more marked so that on February 27, 1934, she again applied for admission.

Physical examination on admission disclosed a young, well nourished negress lying comfortably in bed. Oral temperature was 98.2° F, pulse 90 per minute, respiration 18 per minute, blood pressure 178 systolic and 100 diastolic (right), 180 systolic and 100 diastolic (left). There was no apparent puffiness of the face. Pupils were equal and regular and reacted to light and accommodation. The ocular fundi revealed no remarkable changes. Oral hygiene was good. The tonsils were enlarged but not reddened. The breasts were lactating, the lungs clear. The heart was not demonstrably enlarged. The sounds were clear. A_2 was greater than P_2 . Sinus arrhythmia was present. No murmurs were heard. The abdomen revealed only a small umbilical hernia. Vaginal examination disclosed the fundus anterior, and the cervix bilaterally lacerated. No tenderness and no adnexal masses were palpated. The lower extremities revealed pitting edema extending up to the knees.

Laboratory Work Urinalysis disclosed a specific gravity of 1.032, albumin ++++ (10 per cent wet), numerous casts and red blood cells, many white blood cells (catheterized). The phenolsulphonephthalein was 30 per cent in two hours. On March 5, 1934, an Addis count (catheterized) showed casts 38,500, red blood cells 770,000, white blood cells 1,925,000. Non-protein nitrogen was 28, blood sugar 92 mg per cent, hemoglobin 80 per cent, and red blood cells 4,100,000. The Wassermann test was negative. Feces were negative for ova and parasites. The electrocardiogram showed no evidence of myocardial disease. Roentgen-ray of the chest disclosed clear lung fields, a transverse diameter of the chest of 27.2 cm, a transverse diameter of the heart of 13.5 cm. Cystoscopic examination (March 12, 1934) of the right kidney disclosed 10 to 20 red blood cells per high power field, 10 to 20 white blood cells per high power field, of the left kidney, 20 to 30 red blood cells per high power field, no growth on culture.

The albumin and red blood cells gradually diminished in amount until, on March 17, 1934, none were found in the urine. Small numbers of white blood cells remained. With the changes in urinary findings the edema disappeared and the blood pressure gradually dropped to 120 systolic and 80 diastolic. On March 17, 1934, the patient was discharged to her physician in an outlying parish.

*Case 7** M. T., a colored primipara, aged 26 years, had been followed in a prenatal clinic and found to have a normal physical examination, blood pressure and urinalysis. Subsequent term delivery was uneventful and without instrumentation. Four days postpartum the temperature rose to 101° F and returned to normal four days later. No localizing signs of infection were found. Lochia were normal. She was discharged to her home on the eighth day and 14 days later, 22 days following delivery and 18 days after the febrile puerperal episode, edema suddenly appeared in the face, feet and legs. Two days later the abdomen became distended. The urine was scanty and grossly red. Physical examination revealed a typically distributed nephritic edema, a blood pressure of 168 systolic and 102 diastolic, normal appearing tonsils, lactating breasts and negative lung findings. The heart was not demonstrably enlarged. Rhythm was regular, P_2 was greater than A_2 . There were no murmurs. Venous pressure was normal. Ascites was present. Urinalysis showed 26 per cent albumin (moist), many fine granular casts and numerous red blood cells. Cervical culture disclosed hemolytic streptococcus and staphylococcus. The Wassermann was negative. Following a stormy course with hypertensive encephalopathic

* This case has been reported previously in Trans Assoc Am Physicians, 1937, 111, 198

attacks, the symptoms, signs and urinary findings cleared and the patient was discharged

Case 8 O H, married negress, aged 34, entered the hospital on December 2, 1933, complaining of shortness of breath. Her health in the past had been generally good. There was no history of sore throats, scarlet fever, cyanosis, dyspnea nor edema, except as stated below. There had been 11 pregnancies with all of which slight ankle edema was noted. Never had there been any symptoms of toxemia of pregnancy. Hypertension had never been noted and, when in this hospital with a pregnancy in June 1928, the laboratory findings, physical examination and blood pressure were normal. A pregnancy terminating in the delivery of normal twins on October 2, 1933, was accompanied by no symptoms except the usual slight ankle edema. However, several days following the delivery the patient became suddenly short of breath and was relieved only by sitting up. Palpitation accompanied the attack of dyspnea. Similar attacks occurred several times daily, lasted 15 to 30 minutes, and were relieved only by assuming the sitting position. During these attacks a severe feeling of oppression was felt substernally and a dry hacking cough developed. The edema of the ankles, which in previous pregnancies had quickly subsided on bed rest, not only remained but extended from the ankles to the thighs and abdomen. Dyspnea, at first paroxysmal, became evident at all times. Rest in bed and medication at home were of no avail so the patient applied for admission to the hospital.

Physical examination on admission disclosed a 35 year old negress lying propped up in bed and breathing with difficulty. The pupils reacted to light and accommodation. The retinal vessels showed moderate sclerosis only. The thyroid gland was not palpable. The mouth showed poor oral hygiene with many carious teeth and a foul breath. On examination of the lungs the breathing was found to be symmetrical but labored. Coarse râles were heard in both bases. The bases failed to descend with respiration and impairment of resonance, with diminished breath and voice sounds, was noted. The heart was demonstrably enlarged. The left border of cardiac dullness was percussed 16 cm to the left of the midsternal line in the fifth left interspace. M_1 was muffled. There was a blowing localized systolic mitral murmur which did not replace the first sound. P_2 was greater than A_2 and loud and tambour-like. Occasional extrasystoles were heard. Blood pressure was 138 systolic and 116 diastolic. The abdomen was distended. A fluid wave and shifting dullness were elicited. The liver edge was felt 5 cm below the costal margin. External genitals were negative. The perineum was relaxed. Pelvic examination disclosed a congested cervix which was enlarged and bilaterally lacerated. A mucopurulent discharge was present. There were no adnexal masses nor tenderness. Moderate arteriosclerosis was present in the extremities. There was pitting edema of the lower extremities to the thighs. Sacral edema was also present.

Laboratory Work Urine (voided) showed only a trace of albumin. Addis count (catheterized) showed no casts, pus cells 2,252,000, red blood cells 247,580. Phenolsulphonaphthalein was 25 per cent in two hours. Examination of the blood showed hemoglobin 70 per cent, red blood cells 3,250,000, white blood cells 5,250. The differential formula was normal. Non-protein nitrogen was 28, creatinine 12, blood sugar 100 mg per cent. Wassermann and feces were negative. The electrocardiogram showed low voltage QRS in all leads, prominent and notched P_2 , inverted T_1 and T_2 . Roentgenogram of the chest disclosed evidence of fluid in both pleural cavities. This made cardiac measurements inaccurate but the heart appeared definitely enlarged.

The patient reacted well to treatment directed toward congestive heart failure and, by December 8, 1933, became symptom free and free from edema. On December 16, 1933, she was discharged to the Out-Patient Department for treatment.

Case 9 J R, aged 25, married negress, entered the hospital on February 7,

1934, complaining of shortness of breath. Her health in the past had been generally good. There was no history of sore throats, scarlet fever, syphilis nor manifestations of the rheumatic syndrome. On March 6, 1927, she was confined at another hospital. All findings, including the Wassermann, were then negative. Four years previously she complained of pain in her legs which later became swollen. Both knees and ankles felt stiff and she was unable to walk because of the pain. There was no fever nor other symptoms which could be elicited. A doctor advised elastic stockings which she wore for several weeks, after which she felt perfectly well.

On December 3, 1933, the patient gave birth to a normal seven pound child. The delivery by a midwife was accompanied by no dystocia, and no instruments were used. This, as three previous pregnancies, was accompanied by no untoward symptoms whatsoever. No edema nor dyspnea was ever noted. The lying-in period was uneventful. No fever nor chills were noted and the patient got up on the seventh day and began to do her housework. The lochia were normal, as she described them.

Twenty-one days following delivery she was seized with violent colicky pains around the umbilicus, so severe that she had to lie down, double up, and scream with pain. There was no radiation. The pains lasted about an hour and gradually disappeared. She went to sleep to be awakened several hours later with marked dyspnea relieved only by sitting up in bed. There was no associated pain. The attack lasted about half an hour, when she was again able to lie down and sleep. No shortness of breath on exertion was noted on the next day, but two days later she noted some dyspnea on doing her usual housework. The paroxysmal dyspnea recurred nightly and within 10 days dyspnea was present when at rest during the day and she could no longer lie down. The ankles and abdomen began to swell. On February 3, 1934, she began to notice a brownish foul vaginal discharge. Edema became very severe and she was admitted to Charity Hospital on February 7, 1934.

Physical examination on admission revealed a young negress lying propped up in bed breathing rapidly and shallowly, and apparently gravely ill. The skin was cold and clammy. The pulse was rapid and thready and the blood pressure could not be obtained. Hurried examination revealed pulmonary edema, enlargement of the liver and dependent edema. Treatment was instituted with intravenous digitalis, morphine, heat, and 50 per cent glucose. In two hours the pulse was 103, temperature 99.8° F, and blood pressure 145 systolic and 100 diastolic. Four hours later the pulse was 102 and of good volume. Dyspnea was less marked.

More complete physical examination the next day revealed the following pertinent points: temperature 101° F, pulse 56 per minute, respiration 20 per minute. The left pupil was irregular. The tonsils were not inflamed. Breasts were lactating. Lungs showed moisture at both bases. In examining the heart the apex beat was neither seen nor felt. The left border of cardiac dullness was found 7.5 cm from the midsternal line in the fifth left interspace. P_2 was greater than A_2 . A soft systolic murmur was heard in the tricuspid area. The sounds were clear and distinct. The rhythm was irregular in that every third beat was dropped. The blood pressure was 140 systolic and 90 diastolic. Examination of the abdomen disclosed the liver border 4 cm below the right costal margin. Shifting dullness was elicited. There was a small umbilical hernia. The external genitals were normal. The cervix was bilaterally lacerated. The uterine fundus showed subinvolution. No adnexal tenderness nor masses were found. The extremities showed pitting edema two-thirds of the way to the knees.

Laboratory Work Urinalysis showed specific gravity 1.013, albumin heavy trace, infrequent coarse granular casts. A concentration test on February 16, 1934, showed ability to concentrate to 1.013. Phenolsulphonephthalein output on January 9, 1934, was 10 per cent in two hours. Addis count (catheterized) on February 21, 1934, showed 462,000 red blood cells and 63,000 casts. Examination of the blood showed red blood cells 5,180,000, white blood cells 8,250. The differential formula

was normal. Non-protein nitrogen was 35, urea nitrogen was 18, creatinine 1.3 mg per cent. The Wassermann was negative. Blood cultures (three) were negative. An electrocardiogram on February 10, 1934, showed 3:1 partial heart block (digitalis), and moderate left ventricular preponderance. On February 19, 1934, the block had disappeared. A teleroentgenogram disclosed a transverse diameter of the chest of 24.4 cm, a transverse diameter of the heart of 17.0 cm.

By February 14, 1934, the albuminuria had disappeared and the blood pressure had dropped to 120 systolic and 80 diastolic and remained in normal range. The phenolsulphonephthalein output gradually increased to 35 per cent in two hours on January 19, 1934. The edema gradually disappeared and the patient felt well subjectively. The nocturnal dyspnea disappeared and the patient signed her own discharge on February 25, 1934.

*Case 10.** J. N., a colored sextipara, aged 31 years, had no knowledge of her illness until a routine examination while four months pregnant revealed high blood pressure. There were no symptoms until the ninth month, when blurring of vision and vertigo developed. Dyspnea occurred only on unusual exertion. Twins were delivered at term without instrumentation. There were no postpartal symptoms suggestive of sepsis and she remained in bed two full weeks. Twenty-five days postpartum paroxysmal nocturnal dyspnea developed. Dyspnea on slight exertion became evident and dependent edema appeared. Previous pregnancies had been entirely asymptomatic. Physical examination disclosed a blood pressure of 200 systolic and 128 diastolic, the typical retinal findings of diastolic hypertension, "hard exudate," arterial narrowing and irregularity, venous compression and beginning macular star in the left eye. The heart was enlarged, P_2 was accentuated, a systolic apical murmur and protodiastolic gallop rhythm were present. Basal râles, enlargement of the liver, dependent edema and elevated venous pressure were easily demonstrable. The urine disclosed a slight trace of albumin, an occasional fine and coarse granular cast and no red cells. Concentration reached 1018 by the Fishberg technic. The Wassermann was negative. Electrocardiograms disclosed slurring of R_1 and R_2 and inversion of T_1 and T_2 . Routine care with rest and digitalis cleared the patient of signs of congestion. Heart size remained unchanged.

NEPHRITIC GROUP

Inspection of Case Reports 1 through 7 will disclose the diagnostic criteria for diffuse hemorrhagic nephritis, including significant hematuria, albuminuria, casts and edema, coupled with vascular changes and evidence of renal insufficiency. In addition to these findings, peculiar to all diffuse hemorrhagic nephritis, there are striking similarities in these cases in their relationship to the puerperal state. Each patient had been followed in the prenatal clinic with histories, physical examinations, repeated blood pressure determinations, and urinalyses. In no instance was there evidence of vascular or renal disease antepartum. Clear evidence of sepsis invariably appeared within five days following delivery and in two to three weeks, typical acute diffuse hemorrhagic nephritis was evident.

Nephritis in pregnancy, especially its relationship to and differentiation from toxemias peculiar to pregnancy, has long been a major problem. Clarification is progressing, especially since the introduction into the problem by recent investigators of the more satisfactory classifications of Bright's diseases. Reports of cases classified in this way are confined

* This case has been reported previously in *Trans. Assoc. Am. Physicians*, 1937, III, 198.

chiefly to the antepartal period, and reports of nephritic symptoms arising postpartum without objective antepartum manifestations are extremely difficult to find. In those that do exist, the relationship to pregnancy is not described^{1,2}. The more important papers and monographs^{3,4,5} on nephritis do not recognize nephritis dependent on a complication of the puerperium and occurring as a sequel to that complication.

In these seven patients, a relationship to the delivery is not undeniably established. The sequence of events—presumably normal patient, delivery, evidence of sepsis, usual latent period between sepsis and nephritis, followed by the development of nephritis—is highly suggestive. There remains to be shown the nature of the puerperal septic process and its relationship, if any, both to the delivery and to the nephritic manifestations.

A relationship of sepsis to nephritis has long been suspected and postulated. Although the etiology of diffuse hemorrhagic nephritis is unknown, its close and frequent association with streptococcal diseases, such as tonsillitis, scarlet fever, bacterial endocarditis (aside from embolic nephritis) suggests this organism as the etiologic agent. In addition, the streptococcus is intimately associated with puerperal morbidity and is almost singly the cause of grave puerperal sepsis. Since this organism is concerned both with puerperal sepsis and hemorrhagic nephritis, and since both these processes were apparent in our patients, the answer to the pathogenesis of the clinical picture may lie in a study of this organism.

Bacteriologic studies to disclose the presence of the streptococcus immediately suggested themselves as means of confirmation. We isolated this organism from the uterine secretions only once in seven cases, a frequency not differing from the incidence of positive cultures in the absence of nephritis⁶. These cultures were made from the cervix two to three weeks postpartum, at a time and a site where one would not necessarily expect to find the causative organism. Parametritis and endometritis, both commonly occurring postpartum without localizing signs,⁷ may have acted as deep-seated streptococcal infections in the presence of negative cervical cultures.

Nephritis following streptococcal infections usually occurs seven to 14 days after the onset, except in scarlet fever, when it may occur as late as the twenty-first day. In our seven cases, the earliest manifestations which can be interpreted without doubt as nephritic range from 12 to 24 days postpartum. From the fever, interpreted as postpartal infection, the period of latency ranged from 12 to 21 days in all cases except in Case 6, in which symptoms of nephritis appeared 22 days following the first signs of urinary tract infection. If any signs of genital tract infection occurred, they were masked by those of the pyelitis and the time interval may be too long. Clinically, this period of latency, approximately three weeks, from signs of postpartal infection until the development of nephritis, is extremely significant evidence of a direct relationship, particularly since, in all other cases of hemorrhagic nephritis entering the wards during the same interval, there

was no close relationship to pregnancy and no cases occurred which would produce a continuity of days of latency above 22, a distinct break occurring from 22 days to eight months postpartum

Age, parity and the type of delivery appeared to have little to do with the clinical picture. Six of the patients were below 26 years of age, the seventh was 38. Four were primiparae. Two were forceps deliveries, one an abortion, and four delivered spontaneously under aseptic technic in the Charity Hospital.

The outstanding difference between the clinical picture in this group and in nephritis unrelated to pregnancy was the prominence of diastolic hypertension and its symptoms. While hypertension is a prominent symptom in all acute glomerular nephritis, the findings in the present group were uniformly outstanding, and often, along with cardiac symptoms, dominated the entire picture. In patients 2 and 5 it appeared to be responsible for the heart failure. Reduction in pulse pressure, protodiastolic gallop rhythm, cardiac dilatation and accentuation of P_2 are representative of the cardiac manifestations. Low voltage and T-wave inversion characterized the electrocardiogram. These cases resemble closely the non-nephritic group and have, at times, caused some difficulty in differential diagnosis. In Cases 1, 3, 4, 5 and 7, hypertension was responsible for the marked cerebral symptoms, manifested in the first two by severe headache, and in the latter three by twitchings and convulsions.

Important in differential diagnosis are chronic nephritis and toxemias peculiar to pregnancy. Pyelonephritis and infected hydronephrosis are easily differentiated and cause no confusion. As may be seen in Case 6, however, both nephritis and infected hydronephrosis may occur together and the recognition of both diseases is important. Eclampsia, or preeclamptic toxemia, after labor with no evident signs before or during labor is unusual, but does occur. The older literature records numerous cases past the tenth day, but in modern diagnosis eclampsia past the tenth day is unknown.⁸ In the present group, the onset is far beyond this time limit.

Chronic nephritis is singular in its tendency to manifest itself with exacerbations during the antepartum period. Such patients usually improve after labor when the strain of pregnancy is relieved. At the very time when we see symptoms developing in these patients, the nephritis would probably be receding. In all our cases prenatal examination disclosed no evidence of nephritis and the clinical findings and laboratory data, when the clinical picture developed, were in the main those of fresh disease. In two cases only was there evidence of streptococcal disease, tonsillitis, years before. Were these two patients examples of exacerbations of a nephritis present years before, their general features and relationship to pregnancy remain unaltered.

We have also seen focal nephritis at this time, but the presence of edema and hypertension, as well as urinary findings, rules out focal disease.

NON-NEPHRITIC CARDIOVASCULAR GROUP

Cases 8, 9 and 10 are representative of the group characterized by cardiovascular symptoms and signs postpartum in the absence of demonstrable hemorrhagic nephritis. Eight patients of this type have been seen in our colored female services in the past three years. In the past 10 years many such patients have been seen. Data on such patients have been published from the Charity Hospital by Herrmann and King⁹ in 1930 and by Hull and Hafkesbring¹⁰ in 1937. Although the histories in Cases 8 and 9 reveal no subjective findings antepartum, we had not observed the patients at that time and cannot rule out the possibility of a latent process or objective evidence of disease antepartum. Case 10 had definite evidence of a hypertensive state antepartum, but no evidence of broken cardiac compensation. We have seen an occasional patient of this type who, when followed antepartum, has had evidence of hypertension, or at times other etiologic agents causing heart disease with mild congestive symptoms near term. Usually, however, an etiologic agent causing heart disease and evidence of heart disease have not been demonstrable antepartum. Postpartum diastolic hypertension has often been present.

In pregnancy, strain upon the heart increases progressively to, and reaches its maximum during, labor¹¹ with a release of strain following labor. The frequency of heart failure in pregnancy parallels the strain, and rarely does one find heart failure beginning postpartum except in the presence of some serious vascular accident¹². Yet, in the present group of patients, within 18 to 25 days postpartum, evidence of left-sided then right-sided heart failure, with subsequent congestion of the kidneys, appeared in the absence of demonstrable serious vascular complications. The criteria necessary for the diagnosis of hemorrhagic nephritis were absent.

Symptoms have invariably developed within one month postpartum. Sudden dyspnea, cardiac dilatation, accentuation of P_2 , tachycardia, development of gallop rhythm, low pulse pressure, pulmonary congestion and subsequent peripheral edema have characterized the clinical picture. At times the onset was gradual. Edema has often been the first symptom. It usually progressed to a marked degree, as in the three cases cited, with fluid in the serous cavities. Marked edema, together with cardiac enlargement, protodiastolic gallop rhythm, high diastolic and low pulse pressure were the outstanding diagnostic clinical findings. It is to be recalled that these findings were also present in certain patients in the nephritic group. Such patients with both nephritic and cardiac states may rightfully fall into both groups, and the archaic term "cardiorenal" seems appropriate. The electrocardiographic changes, previously mentioned, were also similar.

Data at present are too meager to state the effects of parity and obstetrical complications. Patients 8, 9 and 10 had had 11, 3 and 3 children, respectively. In all instances, previous pregnancies had produced no similar illness. There were two instances of twins, however, and one of toxemia of pregnancy.

The outcome in general has been good. Indeed, in the non-nephritic group we have witnessed no deaths and can report no autopsy findings. However, Gouley, McMillan and Bellet¹³ have recently reported four cases of this type representing the fatalities in seven such patients. All had serious vascular complications. Necropsy showed "a myocardial degeneration differing from the lesions ordinarily associated with the current classification of heart disease." The lesions were focal, showing acute and subacute phases of myocardial disintegration with hemorrhage and a cellular infiltration. Older lesions showed fibroblastic activity leading to acellular scar formation.

Treatment in our hands has consisted of the routine measures employed in congestive failure—bed rest, digitalization, fluid restriction, diuretics, venesection, mechanical removal of fluids from serous cavities, and symptomatic measures. Response to treatment was not striking and, as a rule, gradual improvement resulted in restoration to activity in several weeks, with reduction of blood pressure to normal range. An occasional patient, such as Case 10, becomes a chronic cardiac invalid with readmission to the ward at irregular intervals for bed rest.

We have emphasized the marked cardiovascular symptoms noted in the first seven cases. These findings often dominate the clinical picture and have in our experience led to confusion between these two groups. It is very likely that the factors responsible for the prominence of the hypertensive and cardiac symptoms in the nephritic group play a part in the development of cardiac failure in the non-nephritic group. In both groups the occurrence of cardiovascular symptoms postpartum is significant and the relationship to pregnancy and the puerperium requires further study. That acute hemorrhagic nephritis may cause such a picture when not postpartal is well known, even to the extreme electrocardiographic changes indicative of cardiac involvement¹⁴. However, the extent and severity of the symptoms were so striking, and the elevation of blood pressure so uniform, that when considered with similar manifestations in the non-nephritic group, the possibility of some force or forces, unknown or idiopathic, directly related to pregnancy, a "postpartal cardiac factor," seems worthy of careful consideration. There may be present an injurious influence or the lack of a helpful factor. According to older medical traditions, a toxin would be suspected. Endocrine or vitamin factors are more likely according to present fashions of thinking. This possibility is further strengthened when we note that similar breaks in cardiac compensation have occurred at similar intervals following pregnancy in women in whom rheumatic and hypertensive heart disease were known to be present, but compensated, before delivery. It appears that a puerpera whose myocardium is already subjected to a strain may, for reasons peculiar to the puerperal state, be precipitated into cardiac failure. The myocardial strain may consist of a previous event or occur *de novo*. If new and transitory, as the hypertension of acute nephritis often is, complete clinical recovery may follow.

The factors peculiar to the puerperal state are unknown. The low voltages seen in the electrocardiogram of patient 8 and the T-wave changes in Cases 8 and 10 have led to the suggestion of "toxic" heart disease. We know of no toxin to cause it. The studies of Gouley et al, however, demonstrate anatomic changes of a distinctive character, unlike those seen in the usual etiologic types of heart disease, and further strengthen the theoretical consideration of a factor peculiar to pregnancy and perhaps to certain other states, for in two cases similar findings were demonstrated in the male.

The frequency of diastolic hypertension in these patients as well as similar cardiac findings in the patients with hypertension of acute nephritis indicates that hypertension may be a factor in the development of this clinical picture. It is important to remember, however, that all patients do not have hypertension. We agree with Gouley, McMillan and Bellet that the clinical picture and the histological findings reported by them are not those of the chronic hypertensive state. That hypertension may contribute to the clinical picture as a precipitating factor is evident.

Aside from the few factors mentioned, many other changes may occur in the ante- and postpartal periods, either as usual or unusual events, and contribute to the cardiac disability seen in the non-nephritic group. The marked changes which take place in endocrine functions at this time suggest themselves as possibilities. One may recall the relationship of the pituitary gland both to the puerperium and to arterial hypertension. Ovarian insufficiency has been linked up with venous hypertension. Villaret, St Girons, and Grellety-Bosviel¹⁵ reported venous hypertension (16 to 35 cm of water) and cyanosis in patients said to have had ovarian insufficiency. While the changes in ovarian function occurring at and after labor might contribute to such a picture, it could hardly be more than a partial explanation. Stieglitz¹⁶ has shown that in the puerperal period, coincidental with the onset of lactation, there occurs an increase in arterial tension in both normal and abnormal patients. These changes occur with a diminution in blood calcium, but the causal relationship between the two is unknown. This influence upon the blood pressure is probably responsible in part for the prominent cardiovascular symptoms in these patients. Metabolic changes, anemia, and vitamin deficiency may occur. Infection may be debilitating. Unknown factors may be important. One must realize as well that the pregnant woman usually curtails her physical activities. Labor, to be sure, adds a great strain, especially to the primipara. This is sudden and followed by a period of only partial activity. The period at which full exercise is usually resumed agrees closely in time with the period in which cardiac failure was precipitated in our cases and may have been an important precipitating factor.

The etiology of this group remains obscure. That some process peculiar to the puerperal state may at times act as a precipitating cause of failure in hearts otherwise damaged, or that the same process, together with other changes which contribute to cardiac strain, such as hypertension and mal-

nutrition, may act together and produce failure in a previously normal heart are possibilities which remain unanswered at present

SUMMARY

Two late puerperal complications, following an interval of apparent health, have been recognized (1) Acute hemorrhagic nephritis Patients without evidence of disease until the puerperal period, developed within three to five days following delivery signs of sepsis followed in 14 to 21 days by the appearance of typical acute diffuse hemorrhagic nephritis (2) Congestive heart failure These patients showed previous to delivery little or no evidence of cardiac failure, but 14 to 25 days postpartum developed frank cardiac failure Possible relationships of both of these groups to labor and the puerperal state have been pointed out

BIBLIOGRAPHY

- 1 ROCKWOOD, R, MUSSEY, R D, and KEITH, N M The clinical study of nephritis in cases of pregnancy, Surg, Gynec and Obst, 1926, xlii, 342
- 2 RITCHEY, J O Report of a case of puerperal sepsis with nephritis, Indianapolis Med Jr, 1918, xxi, 590
- 3 ELWYN, H Nephritis, 1926, Macmillan, New York
- 4 FISHBERG, A M Hypertension and nephritis, 1934, 3rd ed, Lea & Febiger, Philadelphia
- 5 STIEGLITZ, E J Nephritis in pregnancy, Am Jr Obst and Gynec, 1931, xxi, 26
- 6 HARE, R, and COLEBROOK, L Biochemical reactions of hemolytic streptococci from the vagina of febrile and afebrile parturient women, Jr Path and Bact, 1934, xxxix, 429
- 7 DELEE, J B Principles and practice of obstetrics, 5th ed, Saunders, Philadelphia
- 8 JOHNSTONE, R W Postpartum eclampsia, Jr Obst and Gynec British Empire, 1910, xvii, 41
- 9 HERRMANN, G, and KING, E L Cardiovascular disturbances in the obstetrical patient, Jr Am Med Assoc, 1930, xcv, 1472
- 10 HULL, C, and HAFKESBRING, E "Toxic" postpartal heart disease, New Orleans Med and Surg Jr, 1937, lxxxix, 550
- 11 STANDER, H J, and CADDEN, J F The cardiac output in pregnant women, Am Jr Obst and Gynec, 1932, xxiv, 13
- 12 CARR, B F, and HAMILTON, B E Five hundred women with serious heart disease followed through pregnancy and delivery, Am Jr Obst and Gynec, 1933, xxvi, 824
- 13 GOULEY, B A, McMILLAN, T M, and BELLET, S Idiopathic myocardial degeneration associated with pregnancy and especially the puerperium, Am Jr Med Sci, 1937, cxciv, 185
- 14 MASTER, A, JAFFE, H L, and DACK, S The electrocardiogram in acute nephritis, Am Heart Jr, 1936, xii, 244
- 15 VILLARET, M, ST GIRONS, F, and GRELLIET-BOSVIEL, P Peripheral venous tension, Presse Med, 1923, xxxi, 318
- 16 STIEGLITZ, E J Hypertension in pregnancy, Arch Int Med, 1927, xxxix, 465

POSITIVE PRESSURE RESPIRATION AND ITS APPLICATION TO THE TREATMENT OF ACUTE PULMONARY EDEMA^{*}

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THE purpose of this paper is to present observations we have made which provide a physiologic basis for the use of positive pressure respiration in the treatment of acute pulmonary edema. For the most part positive pressure has been thought of as a method of resuscitation such as that accomplished by the pulmator in accidental asphyxia. The function of pressure in the respired air has, however, a broad physiological significance, being employed by the human organism itself as a compensatory mechanism as well as lending itself to therapeutic application in inhalational therapy. We wish to present the subject from the following points of view: (1) A critical discussion of the pertinent literature. (2) Animal experimentation on the development and treatment of acute pulmonary edema. (3) Physiological studies on the effect of positive pressure respiration in human subjects. (4) The clinical results of treatment with positive pressure in patients with acute pulmonary edema.

1 DISCUSSION OF LITERATURE

In 1878 Welch¹ presented his theory of the origin of pulmonary edema in the following words: "A disproportion between the working power of the left ventricle and of the right ventricle of such character that the resistance being the same the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." By squeezing the left ventricle of rabbits between his fingers, Welch observed in many instances forcible contraction of the right ventricle with diminished force of the left ventricle, as indicated by the pressure in the carotid artery, with the result that well marked pulmonary edema took place.

Meltzer² brought apparent confirmation to this hypothesis by producing pulmonary edema in rabbits through the intravenous injection of adrenalin. He explained this occurrence as a result of the considerable constriction of the smaller systemic blood vessels, which presented such an increased burden to the left ventricle that it became unable to expel all the blood which it received from the pulmonary veins, while on the other hand the right ventricle unloaded with increased energy upon the lungs all the blood which the contracting vessels drove into it.

Haven Emerson³ in 1909 showed that pulmonary edema produced by adrenalin could be consistently removed by applying artificial respiration.

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through a tracheotomy tube, gently distending the lungs and allowing them to collapse. The explanation he advanced for the striking improvement in respiration and circulation which occurred was that the full expansion of the lungs due to distention from within forced a considerable amount of blood onward to the left auricle and ventricle, during expiration more room in the pulmonary vessels and a diminished resistance in the lungs allowed the distended right ventricle successfully to empty itself. He suggested as a clinical procedure artificial respiration, raising the arms of the patient above the head and then pressing them across the upper part of the abdomen, believing that this accessory pumping action would facilitate the flow of blood through the lungs.

This suggestion was tried several weeks later by Barringer,⁴ in a patient with cardiac insufficiency who suddenly developed edema of the lungs. At the end of an hour of artificial respiration the signs of edema, rattling in the throat and moist râles had largely disappeared.

In 1897 Norton⁵ had reported a case of edema of the lungs due to carbolic acid poisoning in which a rapid clearance of the edema took place with the use of the Fell-O'Dwyer forced respiration apparatus. Although a theoretical discussion of the mechanism was not made in this report, the clinical result was carefully described and was unmistakably the result of the introduction of a laryngeal tube and the application of forced respirations under positive pressure. (Description of apparatus published by Northrup⁶)

The use of positive pressure as an aid to breathing is described in even earlier literature. Oertel (1878)⁷ employed 20 to 100 inspirations of air compressed to $\frac{1}{80}$ to $\frac{1}{50}$ atmosphere excess pressure in the treatment of severe asthma, and remarked that the dyspnea is relieved while the inflation of air cells is checked by the cessation of the forced inspiratory movements and the rarefaction of air within them prevented. He also had traced the secretion of sero-mucous fluid into the finer bronchi to the violent inspiratory dilatation of the thorax during occlusion of the bronchioles, a concept which our own studies appear to confirm.

The observations of Emerson as to the effectiveness of artificial respiration in abolishing pulmonary edema due to adrenalin were confirmed by Auer and Gates in 1917⁸ and by Johnson⁹. Auer and Gates also showed that tracheal stenosis accentuated the edema caused by adrenalin. When adrenalin was injected in rabbits whose hearts were exposed for inspection and in whom artificial respiration was carried out, they observed the pulmonary artery to be dilated, the left auricle enormously swelled, the left ventricle small, and sooner or later the rate of contraction of the left ventricle became only half that of the right side of the heart. However, despite the apparent fulfillment of the fundamental postulate of Welch's theory, the degree of pulmonary edema produced was slight and even negligible when compared with the marked edema which resulted from the same dose of adrenalin injected into animals whose thorax was intact. Even more

striking edema was produced when the vagi had been divided. The authors rejected Emerson's tentative explanation that distention of the lung by artificial respiration drove a considerable amount of blood into the left auricle and thus relieved the pulmonary congestion, nor did they believe that the edema resulted from back pressure from the left ventricle, since they did not observe any dilatation of the left ventricle or regurgitation in the left auricle. The left ventricle in the rabbit after adrenalin seemed to be in a state of greater tone than normal. They believed that artificial respiration with positive pressure did not exert its inhibitory action on pulmonary edema through action on the heart itself, but that the significant factor involved was the relief of the negative pressure within the chest which exerted a suction action, like dry cups, on capillaries in the alveolar walls.

Although adrenalin relieves bronchial asthma, it had been shown by Golla and Symes¹⁰ that adrenalin in animals produces constriction of the bronchioles unless previous constriction has been produced by other drugs. Since constriction of the bronchial muscles had been experimentally demonstrated as a result of adrenalin injection, Auer and Gates assumed that an increased negative pressure within the chest became necessary during inspiration, producing the cupping action on the alveoli which aided the passage of fluid from the engorged capillaries into the alveoli.

According to these authors, the positive pressure which artificial respiration produced in the lung partially overcame the bronchial constriction due to adrenalin and thus prevented the intra-alveolar pressure from becoming highly negative during inspiration, in that way removing the suction action on the pulmonary capillaries.

Loeb¹¹ in reviewing the evidence just presented came to the conclusion that the reduction of the negative pressure due to insufflation of air into the lung was the important factor in the prevention or amelioration of pulmonary edema produced by adrenalin.

Plesch¹² also made the suggestion that increased pressure in the air passages of the lungs would be valuable in the treatment of pulmonary edema. He mentioned that the effect would be to push the blood already in the pulmonary circuit onwards to the left ventricle and at the same time to oppose the delivery of more blood by the right ventricle, he believed it would be of special importance when the patient's respiration was "rattling," for this was considered by him to be a compensatory mechanism to hinder the edema, the patient makes short inspiratory gasps since the diminished pressure during inspiration is dangerous, tending to cause edema and makes prolonged rattling expirations through the bronchi and glottis which keep up a pressure acting in the opposite direction.

Poulton¹³ reported beneficent results from the use of this technic in some cases of paroxysmal dyspnea ("cardiac asthma") and in bronchial asthma, although no benefit was obtained when there was generalized heart failure.

The production of congestion and edema of the lung as a result of tracheal stenosis was shown by Moore and Binger¹⁴ to be due to the obstruc-

tion during inspiration, for these changes did not take place during expiratory obstruction alone. Barach¹⁵ confirmed these observations and also showed that expiring against a positive pressure created no significant changes in the lung, whereas inspiring against a negative pressure caused congestion and edema, particularly in the lower parts of the lung and areas of emphysema at the periphery. In animals breathing through constricted orifices the negative intrapleural pressure increased as high as tenfold the normal value during the course of a six-hour experiment but when respiration was conducted under a positive pressure of 5 cm. of water, a substantial reduction in the negative intrapleural pressure took place. This was more marked when a helium-oxygen mixture, in which the density was one-third that of oxygen, was employed.

The effect of increased negative pressure on the pulmonary blood flow has been the subject of considerable study, the literature having been reviewed by Tigerstedt¹⁶ and by Wiggers.¹⁷ Daly¹⁸ showed that expansion of the lungs in animals, accomplished by a negative pressure chamber, resulted in an increased pulmonary and peripheral blood flow. Mollgaard,¹⁹ in experiments on the whole animal found similar results. It appeared, therefore, that even relatively marked expansion of the lungs decreased the resistance of the pulmonary bed. When inspiratory obstruction was produced in the cat, Huggett²⁰ found that a marked increase in the minute volume of the heart took place, whereas expiratory obstruction caused the reverse, the blood flow being determined by the Ficke principle.

The sequence of events in the production of pulmonary congestion and edema due to tracheal stenosis may now be postulated as follows. There is an immediate increase in the negative intrapleural pressure which becomes progressively greater. The resistance of the pulmonary bed is lessened and there is at first an increase in the pulmonary and peripheral blood flow. An additional factor promoting increased filling of the right heart may be dilatation of the right auricle. As the intra-thoracic negative pressure increases, blood continues to enter the lungs through the right ventricle but the passage of blood through the lungs into the left auricle and especially from the left ventricle into the extra-thoracic aorta is hindered by the high negative chest pressure. A progressive accumulation of blood in the lungs follows, with a consequent increase in the capillary blood pressure causing a greater filtration pressure outward. Finally, the physical effect of a pathologically heightened negative pressure in the chest exerts a suction action on the capillaries resulting in an exudation of serum into the alveolar walls and spaces, and into the bronchiolar structures as well.

In another group of cases, pulmonary edema may be caused by an increase in permeability of the capillaries to edema fluid. Landis²¹ found that when capillaries are deprived of oxygen for three minutes their permeability to protein is increased. Krogh²² showed experimentally that dilatation of a capillary also increases its permeability. Since anoxemia and pulmonary

edema may occur both these factors may participate. When pulmonary edema is caused by irritant gases such as chlorine in commercial plants and to phosgene in war gas poisoning, the pathogenesis of edema of the lungs may be traced directly to increased permeability. Pulmonary edema as a complication of pneumonia is probably in large part due to an increase in capillary permeability caused by inflammation, probably similar to the irritant inflammation of poisonous gases. However, in many patients with pneumonia the condition is complicated by left as well as right ventricular failure and it is at times difficult to say whether cardiac failure followed pulmonary edema or whether it was present as a contributory cause. An attempt will be made in the clinical section of this paper to analyze the various factors that may have been involved in individual cases of edema of the lungs.

In previous reports dealing with the effect of helium-oxygen mixtures in asthma and respiratory obstruction, Barach²³ pointed out that the use of positive pressure decreases the effort necessary for inspiration and that in patients with asthma the existence of positive pressure during expiration maintains a backward distending pressure which keeps open bronchial and bronchiolar structures that physiologically constrict during the expiratory cycle. This observation suggested the explanation of why patients with asthma and emphysema so frequently pursed their lips during expiration and arbitrarily increased the resistance to the egress of air. This mechanism, developed by the patients themselves, appeared to have the physiological advantage of keeping open bronchiolar passageways, thereby producing a more efficient emptying of the alveolar air. It was suggested that the expiratory grunt in lobar pneumonia was a similar protective mechanism. Furthermore, it was found that patients with more or less continuous asthma of moderate degree will frequently obtain marked relief of their wheezing when they follow the instruction to breathe through partially closed lips for 3 to 10 minutes. The râles in expiration will at times clear up immediately, apparently due to distending the bronchioles through internal pressure. This observation provided an additional stimulus to employ positive pressure respiration in the treatment of acute pulmonary edema, we reported in a preliminary communication three cases in which a swift clearance of the moist râles in the chest took place, even in the presence of advanced circulatory deficiency.²⁴

Since congestion and edema do not occur as a result of expiratory obstruction but consistently follow inspiratory obstruction, the use of positive pressure respiration receives additional support in the treatment of dyspnea due to obstruction. Inasmuch as excessive pressures would obviously prevent the entrance of an adequate amount of blood into the right heart, it was cautioned that this procedure should be followed only with the careful use of manometric readings of the pressure of the respired air.

In the review of the literature above, an essential factor in the production of pulmonary edema, due either to adrenalin or to tracheal stenosis, appeared

to be a heightened negative pressure within the chest exerting a direct suction action on the capillary wall. It is of some interest at this point to remember that Graham²⁵ suggested that the swift formation of pleural exudates in influenzal broncho-pneumonia might be due to a negative pressure within the chest produced by the attempt to inflate the lung through smaller bronchial passages that were constricted by inflammatory swelling.

In the earlier communication²⁴ we reported the rapid clearance of acute pulmonary edema as the result of the continuous application of positive pressure during the total respiratory cycle. Before reporting these results in detail it was thought advisable to study the mechanism more carefully. Although the sequence of events in the production of pulmonary edema following tracheal stenosis seemed clear from the physiological data described above, the type of edema associated with circulatory failure was less easily explained. It seemed likely that additional light could be thrown on the pathological physiology of pulmonary edema due to left ventricular failure if more careful observations were made on experimental edema of the lungs in rabbits due to adrenalin.

2 EXPERIMENTAL OBSERVATIONS ON THE DEVELOPMENT AND TREATMENT OF ACUTE EDEMA OF THE LUNGS CAUSED BY ADRENALIN

Rabbits were anesthetized with evipal intravenously for short experiments and ether by the open drop method in long continued experiments. Adrenalin was injected into the ear veins, the dosage employed being 0.5 c.c. of a 1 to 1000 solution per kg. body weight. Within 15 seconds after the injection the majority of animals stopped breathing for a period of 15 seconds to 2 minutes. In some instances the rabbit died during this period before the development of edema. Autopsy then revealed massive pulmonary congestion. When the animal began to breathe again the respiratory rate was extremely rapid and shallow and generally within 2 to 5 minutes pulmonary edema could be clinically recognized, either by palpation or auscultation. Before the death of the animal a foamy, frequently blood-tinged, fluid exuded from the nostrils. Autopsy of the latter animals showed widespread pulmonary congestion and edema. The heart was markedly enlarged, the enlargement being due to a marked dilatation of the right ventricle and auricle. The left auricle was usually moderately dilated. The left ventricle was contracted and showed no evidence of dilatation.

Data included measurements of the intrapleural and intratracheal pressures, the pulmonary ventilation and tidal air, the systolic arterial pressure, venous pressure, pulse and respiratory rates. A total of 100 rabbits were used. All determinations could not be obtained simultaneously on each animal but there were at least 10 observations on each measurement described. A spirometer of small diameter, namely 5.08 cm., was built in order to show recognizable oscillations of the tidal air and measure the pulmonary ventilation of the rabbit. Each millimeter rise in the bell represented a volume

change of 1.96 c.c. A high speed drum was used to record graphically the changes in chest pressures as well as the respiratory tracings.

The arterial pressure was obtained by inserting a needle into the femoral artery and connecting it with a long glass tube containing saline with a small amount of oxalate solution. Venous pressure was measured in a similar way using the femoral or ear veins. Graphic recording of the intrapleural and intratracheal pressure was made possible by a delicate float with an attached pen suspended in a water manometer.

The roentgen-ray pictures were made possible by a special technic used by Dr. Ross Golden in which films could be taken at 10 to 15 second intervals. The rabbits were tied to a board and pictures taken before and at various intervals after injection and after application of positive pressure respiration.

A series of roentgen-ray pictures taken at 15 second intervals after intravenous injections of adrenalin revealed a progressive increase in the size of the heart shadow. This increase was observed as early as 10 seconds after the injection. In the accompanying reproduction (figure 1) it will be seen that the largest transverse diameter of the heart increased from 3.5 cm. before adrenalin to 3.8 cm. one minute after and 4.1 cm. three minutes after. In addition the lung field became progressively darker, indicating the development of pulmonary congestion and edema.

In figure 2 the size of the heart is shown after adrenalin, and after adrenalin with positive pressure. The rabbit was given the usual dose of adrenalin intravenously and the first picture taken one minute later. Positive pressure was applied immediately thereafter by intermittent inflation of the lungs at a rate of 36 times a minute. The lung was expanded by a pressure of 8 to 10 cm. of water, the trachea being connected to a basal metabolism apparatus in which a positive pressure blower was used. The rabbit breathed 100 per cent oxygen in this experiment, although in the majority air only was employed. Expiration was allowed to take place passively. One minute after the injection, the transverse diameter of the heart increased from 3.3 cm. to 4.1 cm. After three minutes of positive pressure breathing, the heart size was slightly smaller, 3.9 cm. in transverse diameter. The animal was killed five minutes later. Considerable passive pulmonary congestion was found but no evidence of edema.

Figure 3 shows the effect of intermittent inflation of the lung superimposed on a continuously exerted positive pressure both during inspiration and expiration. The animal's trachea was connected with a motor blower unit which maintained a positive pressure of 4 cm. during inspiration and 6 cm. during expiration. Intermittent inflation was then added so that the animal experienced a pressure of 10 cm. during inspiration and 6 cm. during expiration. The first photograph shows the normal transverse diameter of the heart to be 3.4 cm. One minute after injection of adrenalin there is an increase to 4.0 cm. The combined intermittent inflation and continuous positive pressure was begun immediately after the second picture and the film taken three minutes later. This showed a marked decrease in the trans-

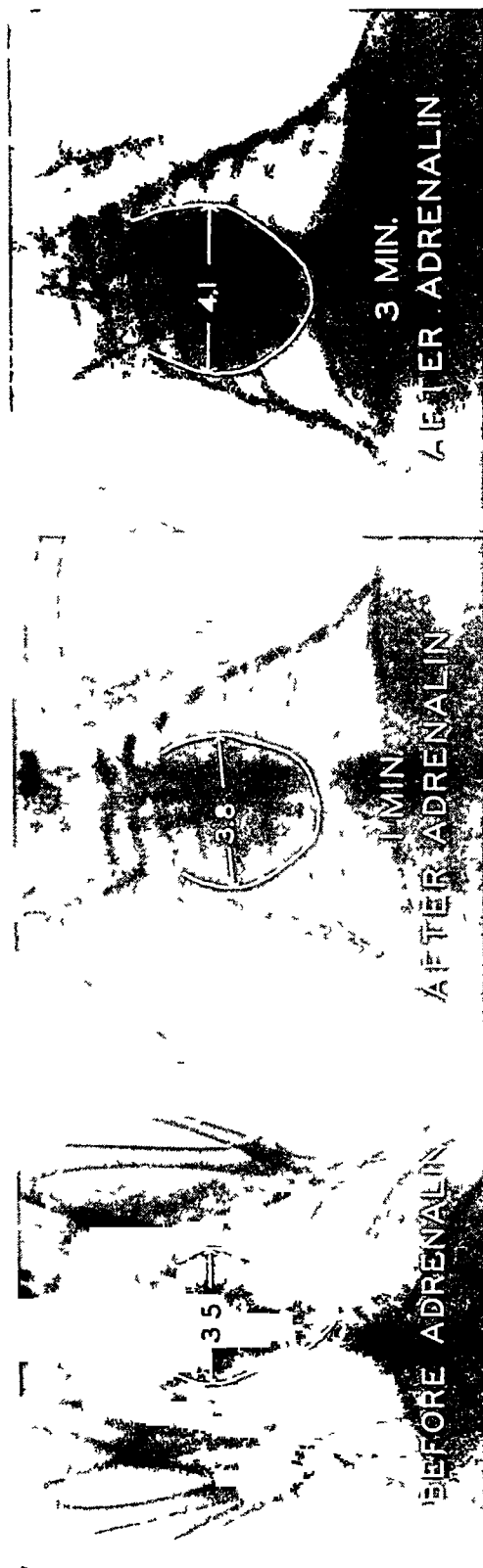


FIG 1 Effect of the intravenous injection of adrenalin on the size of the rabbit heart

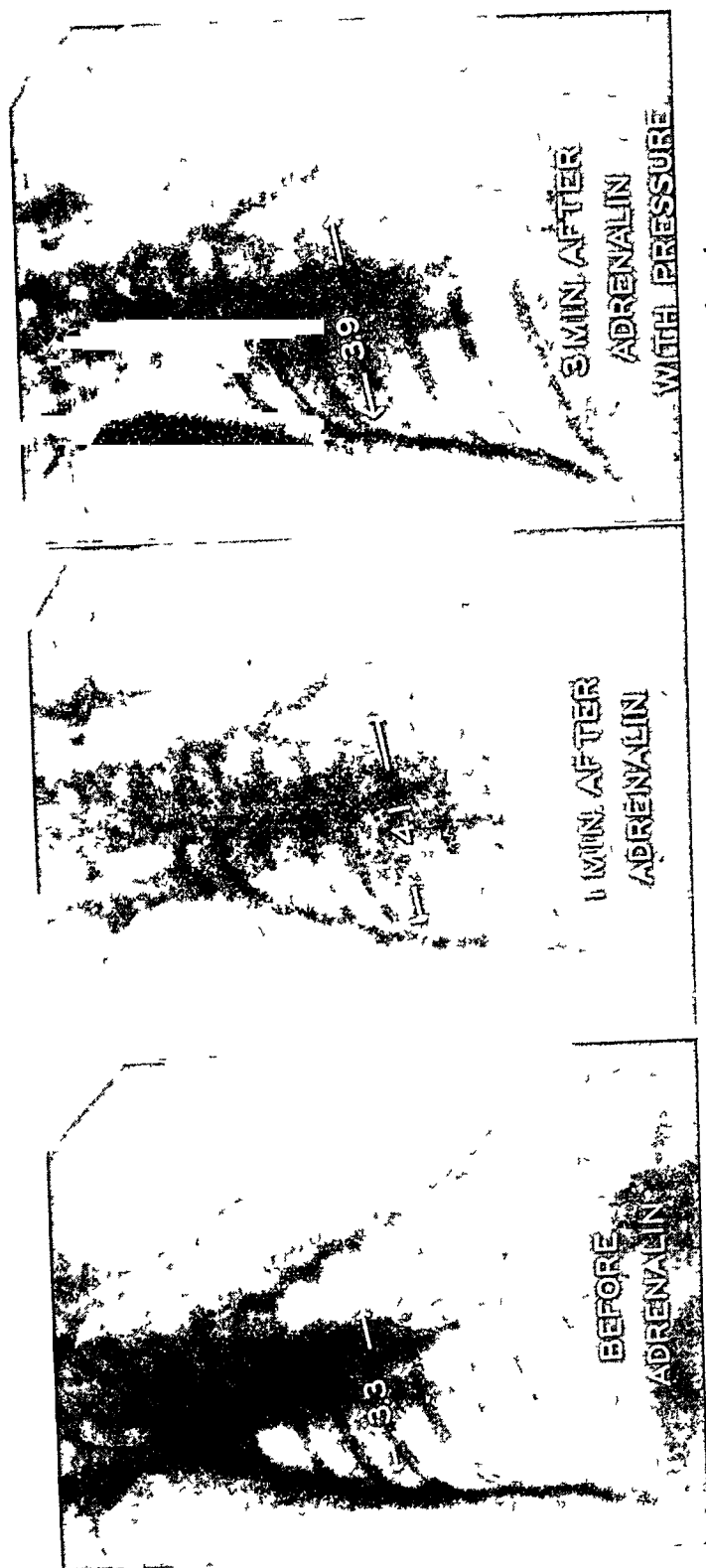


FIG 2 Effect of intermittent inflation of the lung on the size of the rabbit heart after adrenalin

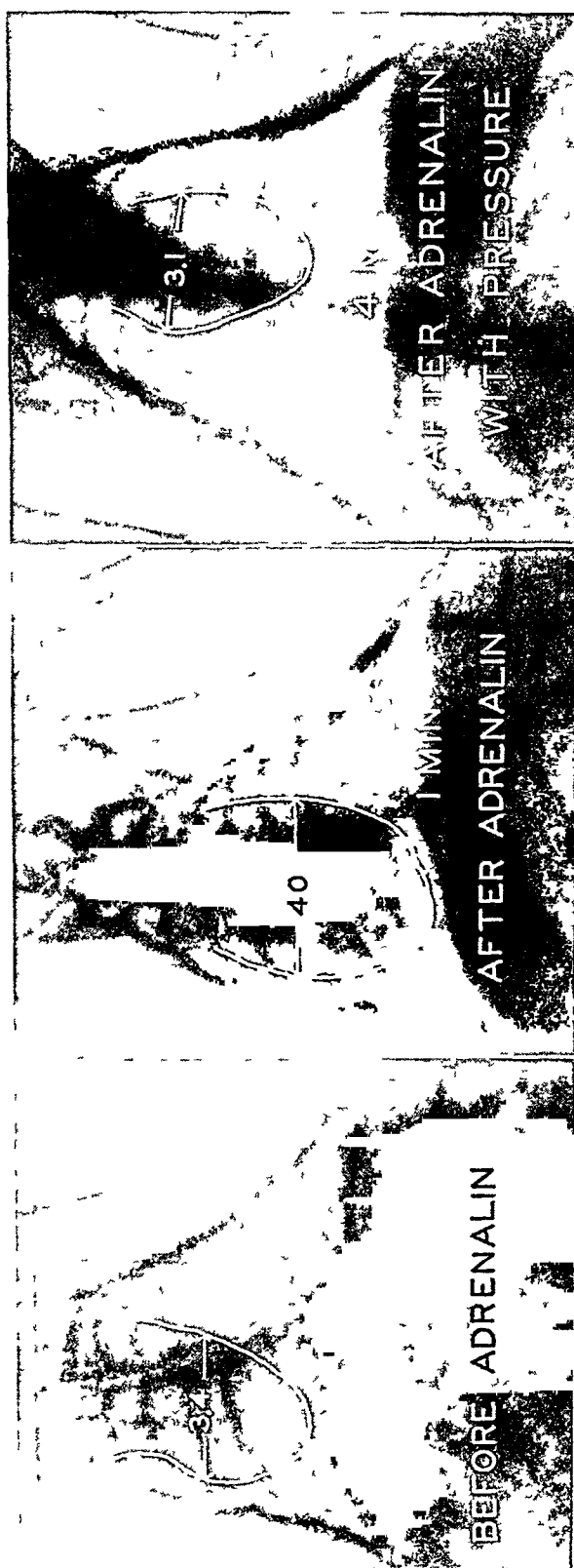


FIG 3 Effect of positive pressure on the size of the rabbit heart after adrenalin

verse diameter of the heart to 3.1 cm. It will also be observed that the lung was expanded, the diaphragm flattened, and the lung field showed an increased radiability. The animal died five minutes later possibly due to the maintenance of excessive pressure interfering with an adequate inlet of blood into the right heart. At autopsy, however, pulmonary congestion and edema were not found.

The three pictures reproduced above illustrate the significant findings obtained by roentgen-ray of the heart. We may summarize these results as follows. Following the intravenous injection of 0.5 cc of adrenalin per kg of body weight, there is a marked increase in the transverse diameter of the heart within 15 seconds. A further progressive increase takes place, reaching a maximum at approximately three minutes after injection. At this time a darkening of the lung shadow, particularly at the bases of the lung, takes place.

When positive pressure is applied by intermittent inflation of the lungs, pulmonary edema may be prevented. When moderate pressures are used, the heart size appears to be slightly decreased. Under these circumstances autopsy shows a dilated right ventricle, passive pulmonary congestion of moderate extent, without edema. When more marked positive pressure is employed, such as is achieved by intermittent inflation of the lungs plus a positive pressure continuously exerted during expiration as well as inspiration, the heart size may become even smaller than it was during the control period. Under these circumstances pulmonary congestion and edema may be prevented. However, the animal may die, if excessive restriction of blood flow is maintained for a long period.

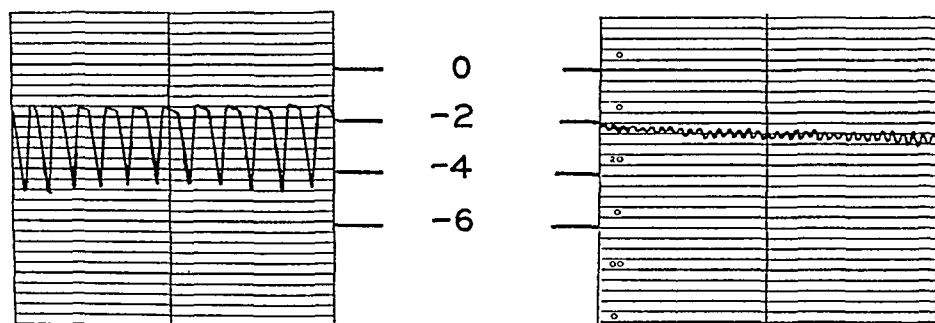
We have not attempted to determine in a precise way the optimal pressures required to control the onset of pulmonary congestion and edema, but have established the fact that pulmonary edema may be prevented by the application of positive pressure respiration of such a degree as to cause a slight diminution in the size of the heart. The possibility presents itself that cardiac dilatation may be controlled by the application of positive pressure respiration in which a decreased entrance of blood into the right heart is accomplished. The danger of an excessive curtailment of total blood flow must of course be kept in mind.

RESPIRATORY MEASUREMENTS AFTER INTRAVENOUS INJECTION OF ADRENALIN IN THE RABBIT

Since it had been assumed that a pathologically elevated negative chest pressure was the important factor in the production of pulmonary edema^{8, 11} it seemed desirable to make direct observations of the intrapleural pressure. In the accompanying graph, the intrapleural pressure of a rabbit before and after adrenalin is shown (graph 1). It will be seen that the intrapleural pressure ranged from approximately -1.6 to -4.4 cm of water during the control period. After injection of adrenalin (1.2 minutes) the range

was exceedingly small, namely about 0.3 cm, the average pressure being -2.4 cm. The respiratory rate increased from 55 to 175.

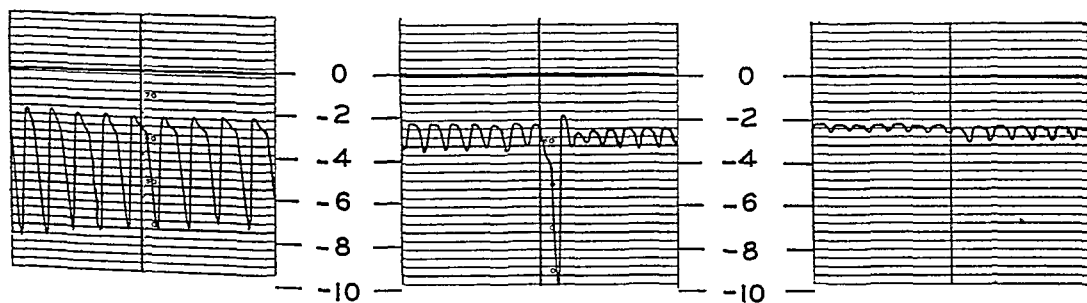
In graph 2, the intrapleural pressure of a rabbit is shown in which there is not only a decrease in the range of pressure but in which the average pres-



GRAPH 1 Effect of adrenalin on the intrapleural pressure of a rabbit
Control
12 min after adrenalin

sure between inspiration and expiration is even less negative than in the control period (graph 2). Thus, the mean negative intrapleural pressure is -4.9 cm before injection of adrenalin, -2.8 cm two and one-half minutes after injection and -2.6 cm five minutes after injection.

The changes produced by intermittent inflation of the lung in a rabbit which had previously been injected with adrenalin are shown in graph 3.



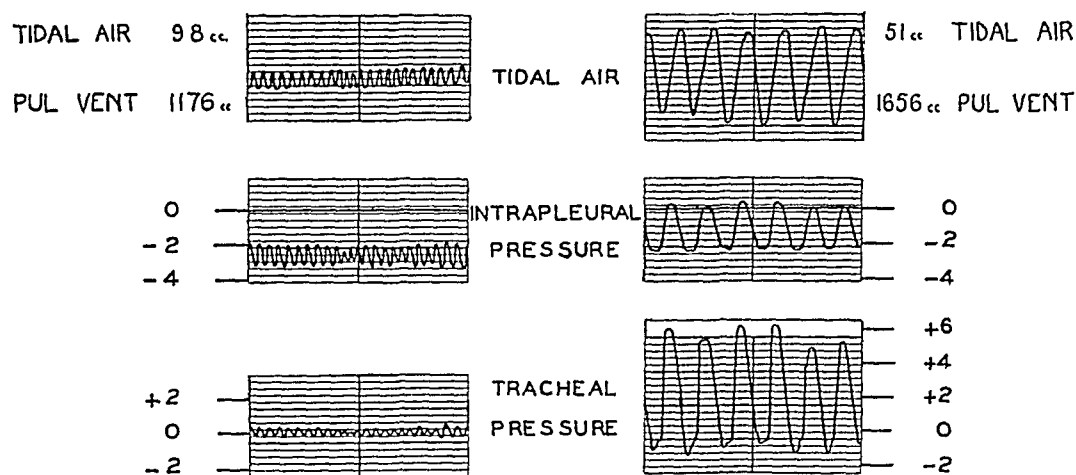
GRAPH 2 Effect of adrenalin on the intrapleural pressure of a rabbit
Control
25 min after adrenalin
50 min after adrenalin

The tidal air was increased from 9.8 to 51 c.c., the pulmonary ventilation from 1176 c.c. to 1656 c.c., the intratracheal pressure from that of the atmosphere to as high as plus 6 cm during the expanding or inspiratory cycle.

The intrapleural pressure rose (as a result of intermittent inflation) from a range of approximately -2.0 cm to -3.2 cm to a range of plus 0.2 cm during inspiration and -2.3 cm during expiration.

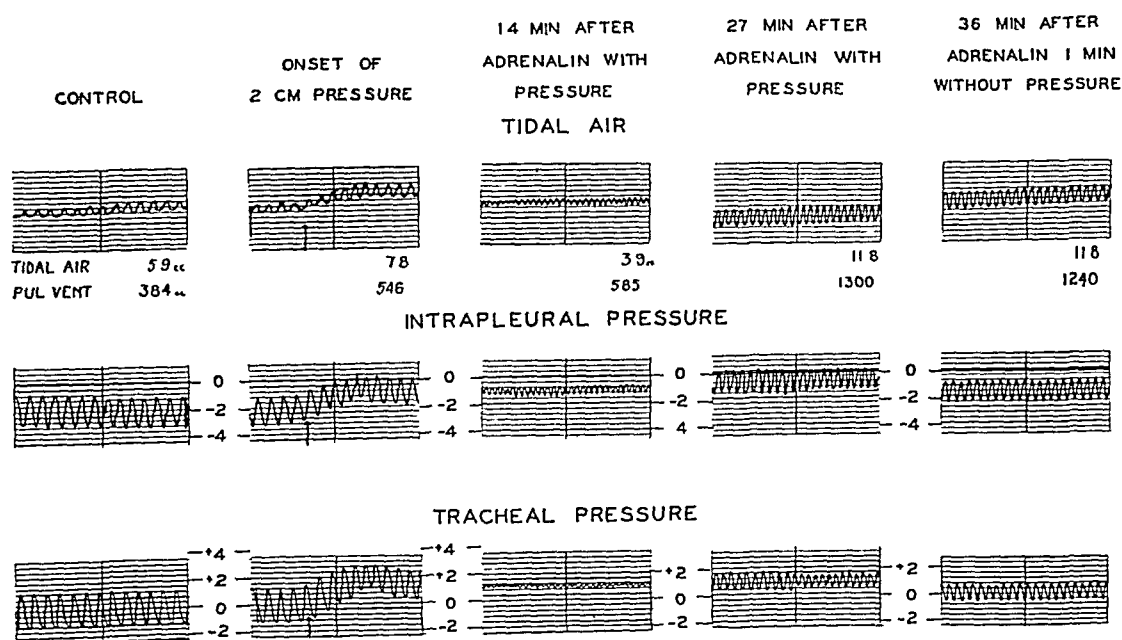
A detailed view of the effect of continuous positive pressure, without intermittent inflation, may be seen in graph 4. The control period shows a tidal air of 5.9 c.c. and a pulmonary ventilation of 384 c.c. After the onset

of a continuous pressure of 20 cm of water throughout the respiratory cycle, the tidal air was 78 cc and the pulmonary ventilation 546 cc. Adrenalin was then injected, with positive pressure continuing. The tidal air dropped to 39 cc 14 minutes later with a pulmonary ventilation of 585 cc. Twenty-



GRAPH 3 Effect of positive pressure respiration on a rabbit after adrenalin
Normal respiration
Positive pressure respiration

seven minutes after injection of adrenalin, the tidal air was 118 cc with a pulmonary ventilation of 1300 cc. Thirty-six minutes after adrenalin and one minute after pressure was withdrawn, the tidal air was 118 cc and the pulmonary ventilation 1240 cc. The animal was autopsied. Pulmonary edema was absent. There was only slight pulmonary congestion. The heart did seem to be dilated.



GRAPH 4 Effect of positive pressure on the respiration of a rabbit after adrenalin

We may summarize the results just reviewed as follows

The characteristic effect of the intravenous injection of 0.5 c.c. adrenalin per kg. of body weight on the respiration of the rabbit is an immediate and marked increase in rate, as high as 175 per minute. The tidal air becomes exceedingly shallow, dropping as low as 1 to 2 c.c. In many instances there is a temporary period of complete cessation of respiration. The extreme shallowness of respiration undoubtedly introduces an anoxic factor, although measurements of the oxygen saturation of the arterial blood were not made. Since capillary permeability has been shown to be increased by anoxemia, this factor may play a rôle in the production of edema.²¹

The significant finding in these experiments is that concerned with the modification of intrapleural pressure. These observations demonstrate that no increase in negative pressure takes place in the intrapleural space as the result of the injection of adrenalin. Observations were recorded on 75 rabbits. The main effect was a consistent and marked decrease in the *range* of intrapleural pressure. The mean point between inspiration and expiration was approximately the same as that in the control period. A pathological increase in the negative intrapleural pressure was only found shortly before death, about 5 minutes after onset of pulmonary edema. At this time the tracheal tree was filled with foaming, blood-stained mucus, the animal resorting to powerful inspiratory gasps in order to suck air into his lung.

The effect of positive pressure whether applied continuously during inspiration and expiration or whether administered with intermittent inflation of the lung was to raise the intrapleural pressure so that it was atmospheric at one phase of the respiratory cycle and approximately — 2 cm. at the other phase.

EFFECT OF POSITIVE PRESSURE RESPIRATION ON THE SYSTOLIC ARTERIAL PRESSURE AND THE VENOUS PRESSURE IN RABBITS AFTER ADRENALIN INJECTION

The systolic arterial pressure was measured by cannulizing the femoral artery and connecting it with a water manometer containing normal saline, the venous pressure was obtained in the same way. Fifteen rabbits were used. The procedure was similar to that employed in arriving at the previous measurements. Determinations were made on the systolic arterial pressure and the venous pressure before and after injection of adrenalin, with and without positive pressure. The results may be summarized in the following charts (charts 5 and 6).

In chart 5 it will be seen that immediately following the intravenous injection of the standard dose of adrenalin, a rise in systolic arterial pressure took place from 79 mm. Hg to 240 mm. Hg. (The pressure was measured in cm. of salt solution and converted into mm. of mercury by calculation.) The arterial pressure then declined, and, if the animal sur-

vived, approached the control level in 15 to 20 minutes. The course of a typical experiment is shown in the graph. The venous pressure generally showed a very slight rise, as shown in the graph, from 55.0 mm of water to 65.0 mm of water. If the animal died there was frequently a further rise of venous pressure of 10 mm. If the animal survived, the venous pressure fluctuated within a range of 10 mm around the control level.

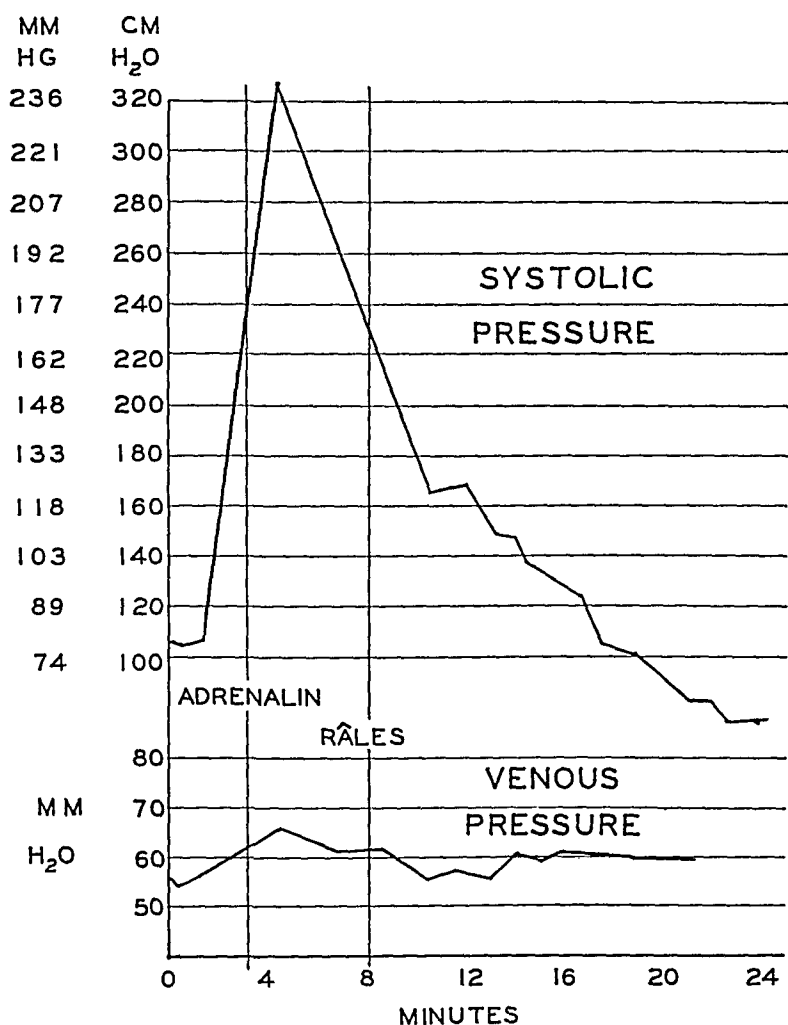


CHART 5 Effect of adrenalin on systolic arterial pressure and venous pressure of normal rabbit

In chart 6 a graphic record is shown of a rabbit breathing under positive pressure, injected with adrenalin, and intermittently treated with positive pressure afterwards. It will be seen that positive pressure respiration of 4 to 6 cm had no noticeable effect on the systolic arterial pressure either before injection of adrenalin or afterwards. The venous pressure likewise showed no effect when the animal breathed under 4 cm positive pressure, but a slight elevation at times took place when the animal was exposed to a pressure of 6 cm of water. The rise in venous pressure was generally no

greater than 8 mm of water, and, *after injection* of adrenalin, this rise sometimes did not take place

The marked rise in systolic arterial pressure, following intravenous injection of adrenalin, was the only noteworthy finding in these experiments. It is of interest that application of positive pressure respiration either by intermittent inflation of the lung, by continuous pressure during inspiration

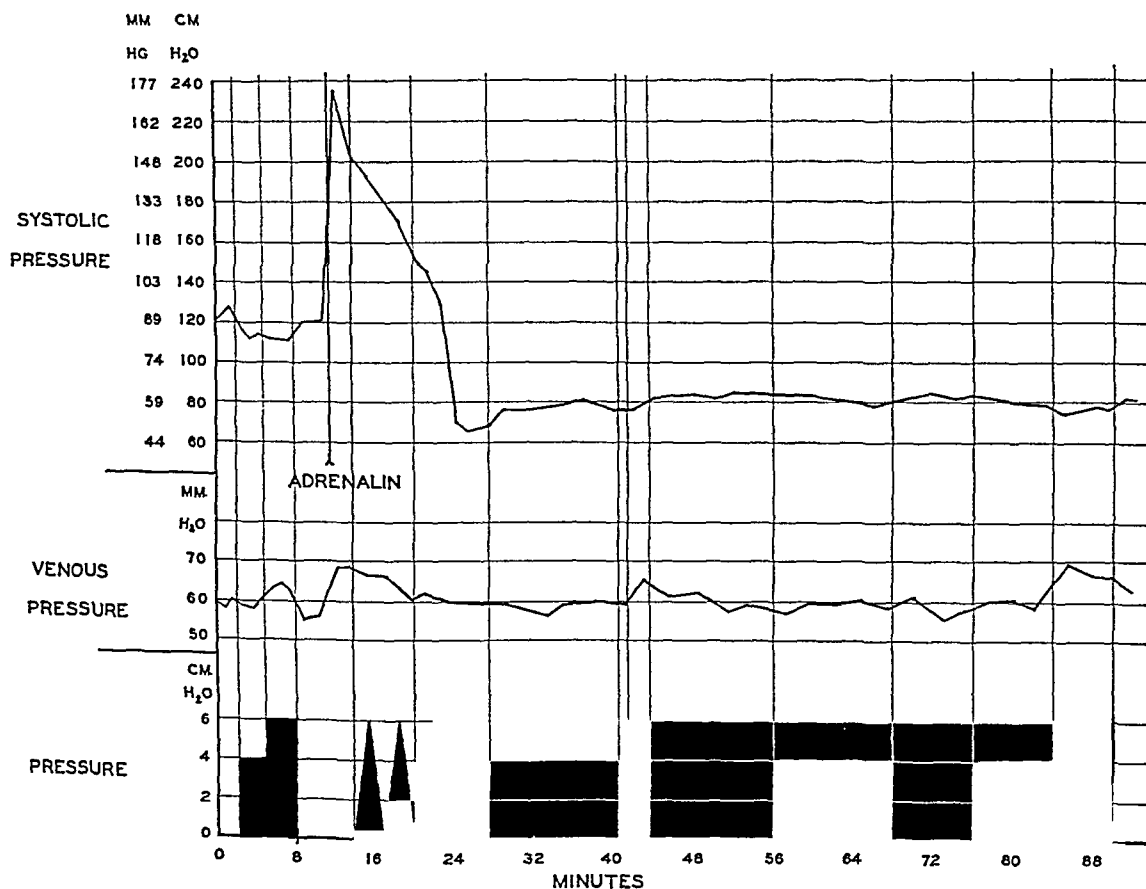


CHART 6 Effect of positive pressure respiration on systolic arterial pressure and venous pressure in a rabbit after injection of adrenalin

and expiration, or by a combination of both methods did not consistently modify the arterial pressure. It should be borne in mind, however, that the dose of adrenalin administered was an exceedingly large one for an animal of this size and that the vaso-constriction produced in the systemic arterial system was probably maximal. It was also surprising that the venous pressure was so little altered, even by respiration under 6 cm of water pressure. We are unable to account for this except on the basis of an increased volume output of blood into the lungs on the part of the dilated right ventricle and a consequent increased diastolic filling of the right heart.

We may now attempt to interpret the pathogenesis of acute pulmonary edema produced in the rabbit by intravenous injection of adrenalin. Our results confirm those of Auer and Gates⁸ and of Johnson⁹ insofar as they

observed dilatation of the right ventricle and right auricle and a contracted state of the left ventricle. There seems to be no doubt that the left ventricle is in a condition of greater tone and smaller volume than the right and that its output of blood per unit of time is less than that of the right ventricle. The left auricle is moderately dilated. We may, therefore, assume that there is less diastolic filling of the left ventricle, its increased tonus being related to the markedly elevated systemic arterial pressure. It was also frequently observed that the right side of the heart contracted periodically, when all movement of the left ventricle had ceased, in animals autopsied three to five minutes after injection of adrenalin.

We were, however, unable to confirm the assumption of Auer and Gates⁸ and of Loeb¹¹ that a pathologically elevated negative pressure was responsible for the occurrence of pulmonary edema. Our measurements showed a smaller *range* of intrapleural pressure, with the mean point between the inspiratory and expiratory intrapleural pressure approximately the same as that present before injection of adrenalin. We believe, therefore, that Welch's fundamental postulate of the cause of pulmonary edema applies to the condition that obtains in rabbits after intravenous injection of adrenalin, namely that there is an inequality in the output of the two ventricles, the right ventricle discharging an increased volume of blood into the lungs, the left ventricle emptying a smaller volume of blood into the systemic arterial system. The fact that the venous pressure is so little elevated under these circumstances confirms the interpretation that the right ventricle is emptying all the blood supplied to it.

In the presence of an increased discharge of blood from the right ventricle and a decreased output from the left, blood accumulates in the capillaries of the lung under increased pressure. This causes the diapedesis of red blood cells which may be observed within one minute after injection of adrenalin. In one-half to one minute later, a serous exudate filters through the capillary wall into the alveolar spaces. Our evidence suggests, to our mind, that the high capillary blood pressure is the significant factor in the pathogenesis of pulmonary edema due to adrenalin. It would seem likely that acute pulmonary edema when it occurs in human subjects as a result of left ventricular failure can be explained by a mechanism similar to the one which we have outlined.

The explanation of the therapeutic effect of positive pressure respiration appears to be more complicated. Although it has been shown in the roentgen-ray studies reported in this paper that dilatation of the right heart could be prevented, as well as pulmonary congestion and edema, by positive pressure respiration, we are not able to conclude that a decreased entrance of blood into the right heart is the sole or even most important factor. Edema of the lungs may be prevented by a degree of positive pressure which only slightly decreases the size of the heart. Furthermore, the application of even moderate positive pressure decreases significantly the mean intrapleural negative pressure. During continuous positive pressure respiration

the intrapleural pressure at the end of expiration is slightly above that of the atmosphere, during intermittent inflation of the lung, the intrapleural pressure during the inspiratory (or distending) cycle of respiration is also slightly above that of the atmosphere. We are, therefore, forced to conclude that the increase in positive pressure within the chest exerts an opposing force tending to hinder the outpouring of both red corpuscles and serum from the pulmonary capillaries. Although anoxemia is undoubtedly present as a result of the extreme shallowness of respiration, and although this is known to increase capillary permeability, the swiftness of development of the condition and the rapidity with which it may be stopped argues against anoxemia as a major influence.

Our experiments therefore lead to the conclusion that both the factors which we have just discussed operate to prevent or stop pulmonary edema. (1) A diminished volume of blood entering the right heart and hence the lung, due to the increased positive pressure within the chest. This in itself would result in a lower capillary blood pressure and, therefore, a decreased tendency for red corpuscles and serum to pass through the capillary wall. It may also be true that an intermittent application of positive pressure might squeeze some additional blood into the left auricle and into the ventricle, with an increased output of blood into the systemic arterial system. Since our studies showed no elevation of systolic arterial pressure under these conditions, we have no evidence to support this hypothesis. (2) The increased positive pressure shown to exist within the chest as a result of positive pressure respiration exerts an opposing force against the capillary wall which physically retards the outward filtration of red cells and serum. (3) Anoxemia is an additional although probably less important factor which increases capillary permeability. Distention of the pulmonary capillaries may also play a part in augmenting capillary permeability.

3. PHYSIOLOGICAL MEASUREMENT OF THE EFFECT OF POSITIVE PRESSURE ON HUMAN SUBJECTS

The physiological effects of positive pressure respiration were studied in normal subjects, patients with congestive heart failure, and in a miscellaneous group. The measurements chosen were the pulse rate, respiratory rate, blood pressure, venous pressure, circulation time and vital capacity. The pressure varied from 3 to 8 cm. of water, administered continuously by means of a rebreathing apparatus consisting of a motor blower unit, a control valve inserted in the respiratory tubing, a water manometer and a soda lime container. The patient was connected to the apparatus by means of a mouthpiece, a mask or a hood with closure at the neck. This has been described elsewhere in detail in connection with helium-oxygen treatment.²⁶ In some cases a basal metabolism apparatus was used with a weight on the bell to give the required pressure.

DATA ON NORMAL SUBJECTS

Ten normal subjects were tested. They breathed oxygen for a control period of five minutes under atmospheric pressure, oxygen under 3 cm water pressure for five minutes, oxygen under 6 cm water pressure for five minutes and oxygen under atmospheric pressure as the final control period.

The *pulse rate* in two of the ten cases showed no change when breathing oxygen under 6 cm pressure. In eight cases, there was a decrease in rate, averaging 7 beats per minute. The *respiratory rate* was slightly increased in two subjects, decreased in three, with no change occurring in the remaining five. No significance can be attached to variations in respiratory rate in these tests. The *systolic and diastolic arterial pressure* also showed no appreciable alteration in the ten tested subjects.

However, the effect of positive pressure on the *venous pressure* was to cause a consistent slight elevation in the majority of instances, thus in eight of the ten individuals breathing against 3 cm of pressure there was an average rise of 10 millimeters of water and in nine subjects breathing against 6 cm of pressure there was an average rise of 20 mm of water (table 1).

TABLE I
Effect of Positive Pressure Respiration on Venous Pressure in Normal Subjects

Subject No	Oxygen Under 0 cm Pressure	Oxygen Under 3 cm Pressure	Oxygen Under 6 cm Pressure	Oxygen Under 0 cm Pressure
1	62	72	88	48
2	52	50	75	42
3	40	54	63	44
4	53	65	76	58
5	160	151	157	
6	67	77	88	60
7	77	83	93	78
8	103	122	125	108
9	68	73	85	70
10	93	101	107	92

The interpretation of this finding appears to be that the increased pressure within the chest produces a resistance to the entrance of blood in the right heart, thus creating a measurable elevation of the pressure in the systemic venous system. This explanation is further confirmed by the results on the *circulation time*, which show in the majority of instances a slight although definite prolongation. Thus, in five of nine subjects there was an average prolongation of circulation time of 3.3 seconds when the subjects breathed against 3 cm of water pressure, and in six out of nine subjects a prolongation of 3.6 seconds when the subjects breathed against 6 cm of water pressure (table 2). The effect of positive pressure, therefore, appears to be a slowing of the velocity of blood flow through the lung (arm to tongue time). From the results on the circulation time and the venous pressure it seems likely that the heart deals with a smaller volume of blood under these circumstances, presumably with a slower total blood flow.

TABLE II

Effect of Positive Pressure Respiration on Circulation Time in Normal Subjects

Subject No	Oxygen Under 0 cm Pressure	Oxygen Under 3 cm Pressure	Oxygen Under 6 cm Pressure
1*	26 0*	9 0*	23 0*
2	19 0	17 8	16 7
3	22 6	26 0	22 8
4	16 4	19 0	20 0
5	20 4	19 8	21 2
6	18 8	18 0	24 2
7	18 2	21 4	22 6
8	19 2	22 6	23 8
9	16 2	20 2	18 5
10	16 0	13 8	17 6

* Taken with saccharin (excluded), other tests done with sodium decholin

The *vital capacity* in nine out of ten subjects showed an average decrease of 350 c c, which may perhaps be accounted for by the fact that there is already an increase in the volume of air in the lungs as the result of positive pressure of approximately 300 to 400 c c when the vital capacity deter-

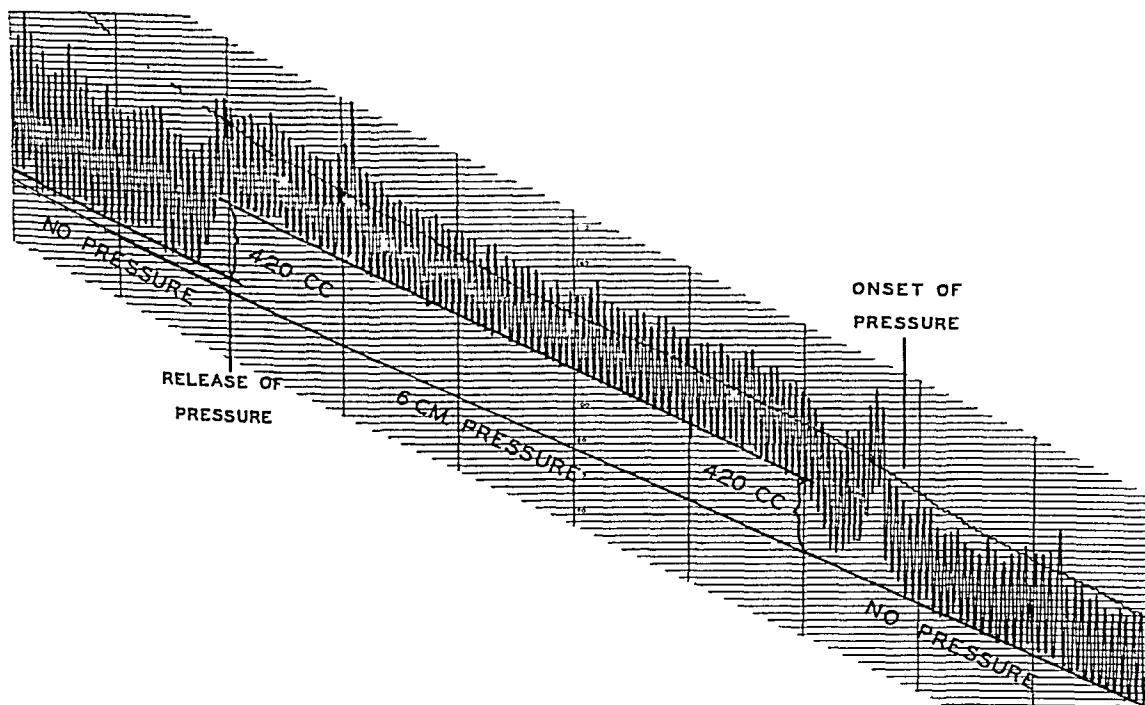


CHART 7 Effect of positive pressure respiration on the volume of gas in the lungs

mination is made. In the accompanying graphic record of the effect of positive pressure respiration on the volume of gas in the lung (chart 7), it will be observed that a normal individual at the onset of pressure took into his lungs an additional 420 c c of oxygen, when the pressure was released, this additional volume of gas left the lung.

EFFECTS OF POSITIVE PRESSURE RESPIRATION IN PATIENTS WITH
CONGESTIVE HEART FAILURE

Fourteen patients with congestive heart failure were tested as to their response under positive pressure. The degree of passive systemic venous congestion (i.e. congestive failure) may be seen from the control venous pressure measurements. The patients were divided into two groups of seven each.* In the first, control observations were taken while the patient was breathing air and oxygen for 5 minute periods at atmospheric pressure. The patients were then switched to breathing oxygen at 8 cm. water pressure for an 8 minute period and observations taken at the end of this time. Additional observations were recorded 3 minutes after pressure was withdrawn, while the patient was breathing air. In the second group, the patients breathed air during the control period, air during the administration of positive pressure (which in this group was 6 cm. of water) and 3 minutes after pressure was withdrawn. The results may be summarized as follows. The *pulse rate* during positive pressure breathing was increased in six cases, averaging 6 beats per minute, decreased in one case, and no change in one case. In the group exposed to 6 cm. positive pressure, the pulse rate was increased in two cases, decreased in three, and no change in two cases. No significance could be ascribed to these changes, psychic influences and perhaps fatigue in all probability overshadowing the physiological influence of positive pressure. The same interpretation can be ascribed to the results on *blood pressure* in both groups. Excluding changes under 8 mm. Hg there were only three instances in both groups in which a marked change was observed. In these cases the systolic blood pressure rose 52 mm. in one case, 30 mm. in the second, and 25 mm. in the third. The diastolic blood pressure rose 38 mm. in the first case, 11 mm. in the second case and 18 mm. in the third case. In the remaining 12 cases the variations were negligible.

The *respiratory rate* in the first group was decreased in five cases an average of 3 breaths a minute, and increased in two, an average of 8 breaths per minute. In the second group exposed to 6 cm. positive pressure the respiratory rate was decreased in all, averaging 9 breaths per minute. The characteristic response to the inhalation under positive pressure is a decrease in the rate of respiration, although it did not occur in all of our cases.

As in the controls, the most consistent changes were in the *venous pressures*. In the group exposed to 8 cm. positive pressure, there was an elevation of venous pressure in seven instances, averaging 43 mm. of water, with a decrease in only one. In the group exposed to 6 cm. water pressure, there was an elevation of venous pressure in six instances, averaging 28 mm. of water, with a decrease in one (table 3). The degree of elevation of venous pressure in the patients with congestive heart failure was greater than in the control subjects who averaged an increase of 20 mm. of water when exposed to 6 cm. of pressure.

* In the first group of seven patients a repeat observation is made on one case, no. 4, so that the data will be presented as if there were eight cases instead of seven.

TABLE III

Effect of Positive Pressure Respiration on Venous Pressure in Patients with Congestive Heart Failure

Case No	Before Application of Pressure		After Application of Pressure	
	Breathing Air	Breathing Oxygen	Breathing Under Pressure Cases 1-7 Oxygen Cases 10-16 Air	5 Minutes After Pressure Was Withdrawn Breathing Air
1	206	184	225	172
2	100	90	190	105
3	65	82	120	65
4	15	15	25	8
4A	5	-8	25	2
5	105	105	90	80
6	74	78	94	73
7	105	93	155	
10	207		230	200
11	88		109	105
12	125		140	100
13	80		120	78
14	180		160	170
15	135		175	165
16	40		70	40

The effect of positive pressure on the *circulation time* was less consistent, perhaps due to the fact that many of these patients were too ill to furnish complete cooperation. Some of them had difficulty in keeping the mouth-piece in place during the entire period and the circulation time was taken within 3 minutes after pressure was withdrawn in these cases. The results may be summarized as follows. In the group exposed to 8 cm positive pressure the circulation time while the patient was on the apparatus was unchanged in two. In two others it was markedly increased, one of them showing a prolongation of 16.5 seconds and the other 10.0 seconds. In the group exposed to 6 cm positive pressure, observations were taken within 3 minutes after pressure was withdrawn. In two cases there was no change, but in three others there was a marked prolongation, averaging 17 seconds. Although lengthening of the circulation time did not occur in all instances, the change when it did take place was much more marked than in the control subjects in whom prolongation of the circulation time when breathing against 6 cm positive pressure averaged only 3.6 seconds (table 4).

The *vital capacity* showed no consistent changes in the group breathing under 8 cm positive pressure. However, in the group breathing under 6 cm positive pressure, approximately 5 minutes after conclusion of the test, there was a rise in six out of seven patients, averaging 216 c.c. The fact that this rise in vital capacity did not occur in the group breathing under 8 cm positive pressure may be accounted for perhaps by the greater fatigue induced in the latter group by a longer experiment. A possible explanation

for the elevation in vital capacity is that some blood was forced out of the lungs into the left heart during the test, allowing greater lung space, although this must be presented only as a tentative hypothesis

TABLE IV

Effect of Positive Pressure Respiration on Circulation Time in Patients with Congestive Heart Failure

Case No	Before Application of Pressure		After Application of Pressure	
	Breathing Air	Breathing Oxygen	Breathing Oxygen Under Pressure	3 Minutes After Pressure Was Withdrawn Breathing Air
1	43 6			53 1
2	45 0		61 5	
3	14 0		14 0	
4	40 0		38 2	32 0
4A	39 0			40 5
5	31 0		41 0	
6	24 0			25 0
7	16 5			24 5
10	32 0			65 0
11	43 0			47 0
12	43 0			44 0
13	54 0			54 0
14	18 0			33 0
15	37 0			
16	23 0			

We wish to present three charts showing the significant changes in typical experiments. In the chart below (chart 8) the effect of breathing against positive pressure is shown in a patient with congestive heart failure. It will be seen that the venous pressure declines during the control period from 205 to 182 mm, begins to rise after the application of 3 cm positive pressure, shows a still more marked elevation at 6 cm positive pressure, reaching 225 mm, and then falls abruptly when the pressure is removed. The circulation time rose from 43 seconds to 53 seconds.

In a patient with asthma (chart 9) the venous pressure rose only slightly with 3 cm positive pressure, from 30 to 40 mm, but rose to a height of 75 mm when 6 cm positive pressure was used, falling to 25 mm when pressure was withdrawn. No significant changes took place in blood pressure or pulse or respiratory rate in any of these cases.

The last chart represents a reaction in a patient with neurocirculatory asthemia (disordered action of the heart) to positive pressure respiration (chart 10). The patient, a young man of 22 years, came to the hospital complaining of breathlessness at rest, palpitation and continuous heart consciousness. He was extremely apprehensive. On examination, his heart showed no abnormalities, the electrocardiogram was normal and roentgen-ray of the heart revealed no enlargement. The test was performed with the

patient in a helmet, a leak-tight closure being made at the neck. Oxygen was breathed throughout. The chart shows that when he was breathing against 2 cm positive pressure, there was a distinct rise in venous pressure

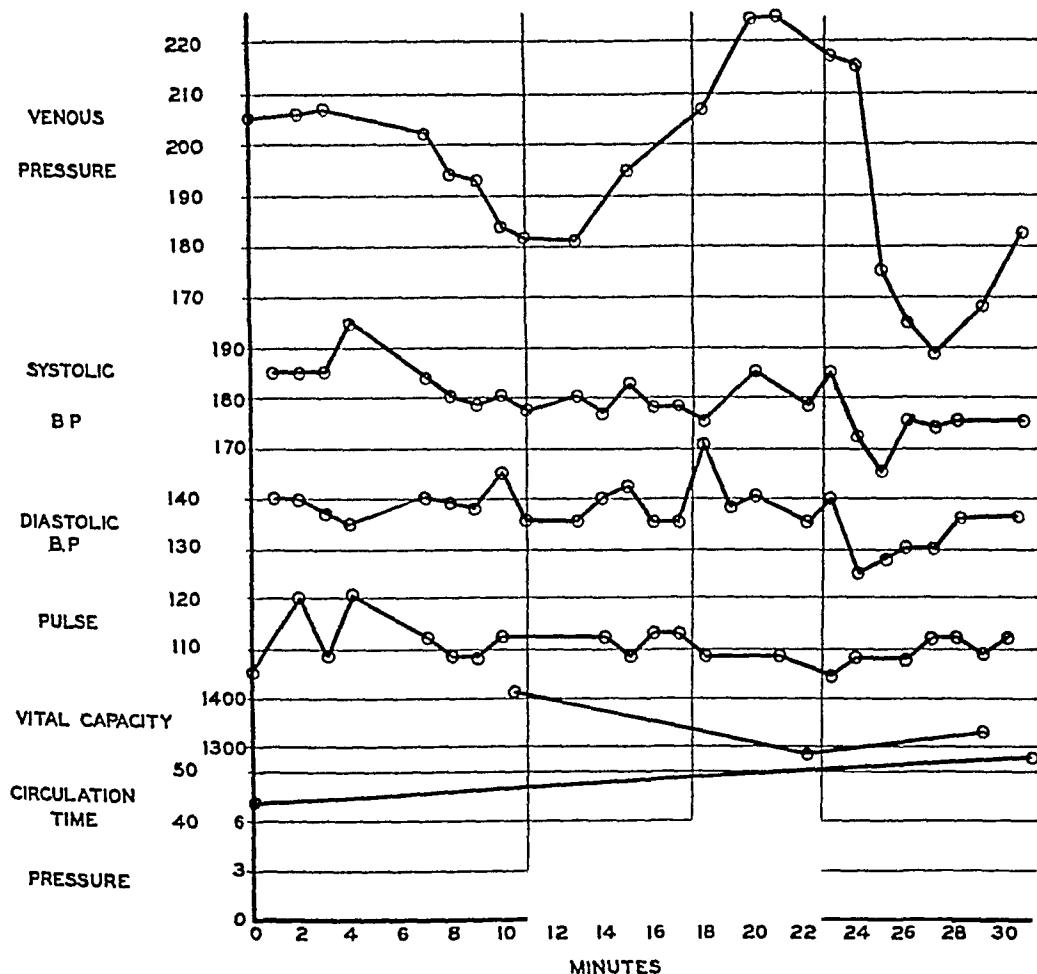


CHART 8 Effect of breathing against positive pressure in a patient with congestive heart failure

on two occasions, from 90 to 120 mm. When the pressure was raised to 5 cm, the venous pressure rose still further to 138 mm and dropped abruptly to 90 when the pressure was removed. The circulation time increased from 18 seconds to 27 seconds while he was breathing under 5 cm water pressure.

This case is of considerable interest in that it portrays physiological changes in a patient whose circulatory symptoms are of nervous origin. In another patient who had anxiety neurosis but without symptoms referable to her heart, the same test showed no elevation of venous pressure when breathing against 2 cm water pressure and no change in circulation time. It would seem likely, therefore, that the rise in venous pressure which occurs after breathing against positive pressure is an indication of an inability of the heart to compensate for an arbitrarily induced back pressure by an increased blood flow. In normal individuals a mechanism exists whereby

the circulation time is only slightly affected by resistance to the flow of blood into the heart, whereas in patients with heart disease, especially congestive failure, marked retardation of the velocity of blood flow may take place

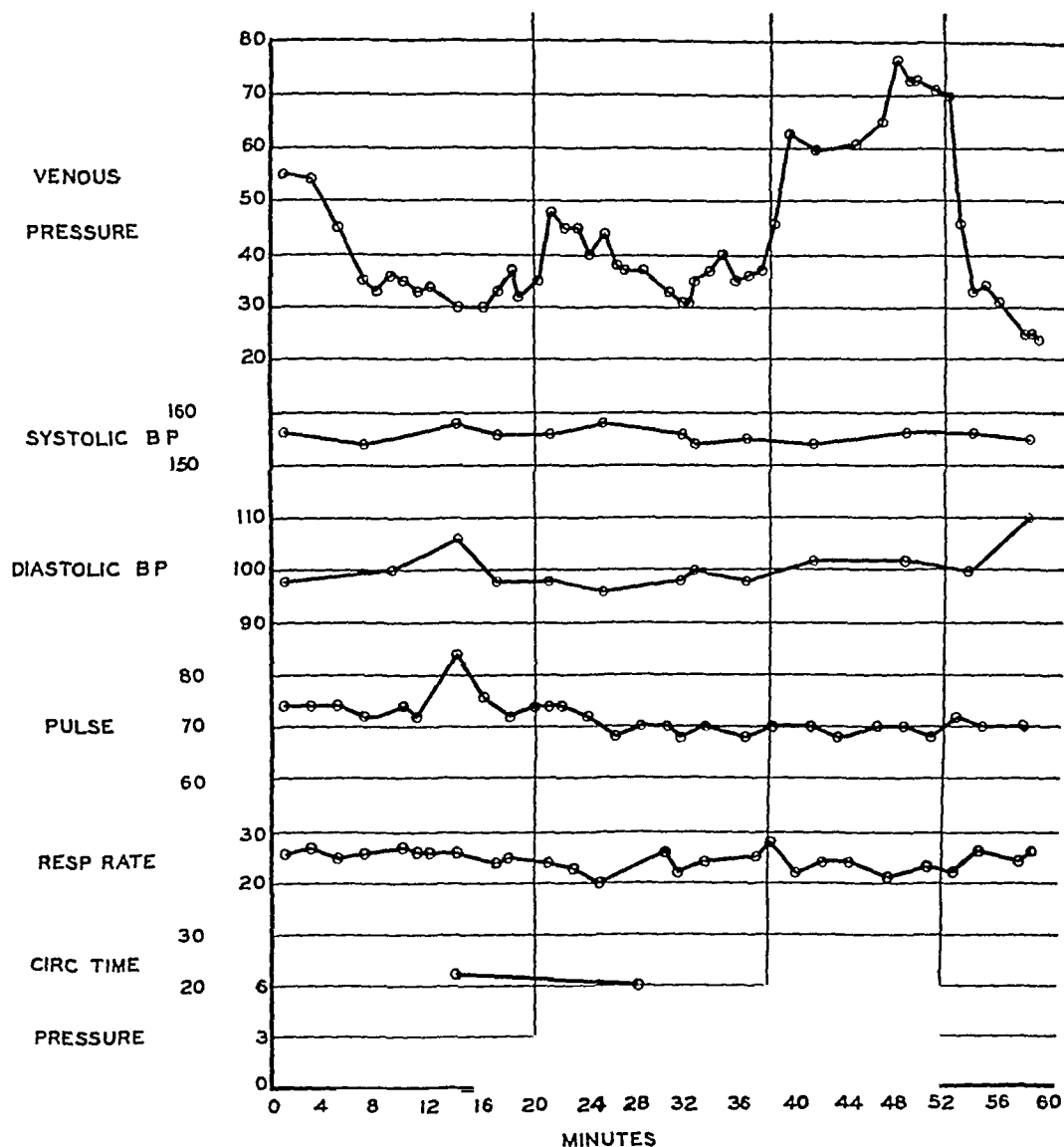


CHART 9 Effect of breathing against positive pressure in a patient with asthma

An explanation of the relatively marked increase in venous pressure and prolongation of circulation time in patients with congestive heart failure exposed to positive pressure respiration invites consideration of several influences. In the first place, the increase of positive pressure within the chest interposes an obvious difficulty to blood entering the right auricle. However, this physical difficulty would appear to be of similar magnitude, other factors being equal, in normal subjects who, however, show comparatively

slight changes It has recently been shown by Christie and Meakins²⁷ that the patient with congestive heart failure has an intrapleural pressure range that is more nearly atmospheric than the normal individual, especially during expiration The presence of so much additional blood in the lungs inter-

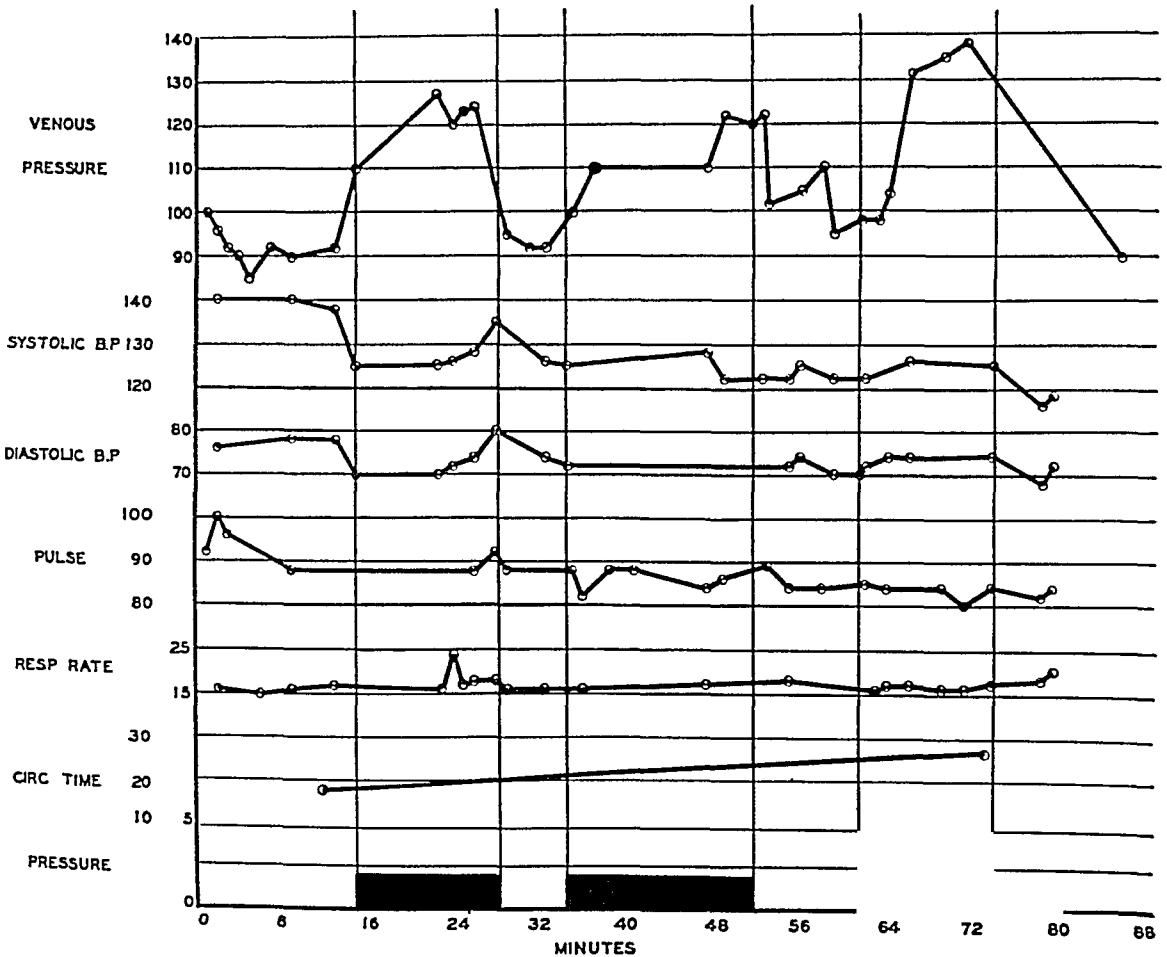


CHART 10 Effect of breathing against positive pressure in a patient with disordered heart action

feres with the elasticity of the pulmonary membrane with the result that the cardiac patient is unable to achieve as high a negative pressure during the inspiratory cycle as the normal person. The cardiac patient would therefore be less able to increase the negative pressure within the chest and so in part lessen the additional positive pressure imposed on the lung from without, whereas the normal individual by an increase in the velocity and depth of breathing could increase the negative pressure within the chest to a degree which would practically overcome the arbitrarily imposed external positive pressure. In this way an explanation is afforded of the relatively small increase in venous pressure and the relatively insignificant interference with the velocity of the circulation that normal individuals show. Some of the variability in our results in patients may also perhaps be explained in

this way, since an individual who because of psychic influences was hyperventilating at the time the circulation test was being made might be temporarily developing an increase in the negative intrapleural pressure which would augment the blood flow. As pointed out in the historical section of this paper, it has been repeatedly shown that an increase in the negative pressure within the chest increases the blood flow both through the lungs and the peripheral circulation.

An additional influence may be set forth, namely, that the presence of an increased positive pressure within the chest interferes with the diastolic filling of the ventricles and the auricles as well, and that this interference would be more apt to have an adverse influence in a diseased heart muscle than in a normal one. It also seems likely that the increased pressure within the lung may in the case of an insufficient right ventricle retard a complete emptying of that chamber of the heart, thus causing a further back pressure of blood into the systemic veins.

We have not discussed up to the present whether this repression of blood into the systemic venous reservoir is an adverse or a beneficial influence. At first sight it might seem that such a slowing of the circulation time would but increase the congestion of the viscera and extremities and thereby accentuate the harmful effects of heart failure. We must consider, however, that this effect is accomplished by decreasing the volume of blood passing through the heart. The heart is at this time dealing with a smaller blood volume which would decrease the burden upon it, and thus have a beneficial influence. One has only to remember the dramatic improvement in some cases with acute congestive heart failure particularly in left ventricular failure that is engineered by withdrawal of 500 c c of blood. Striking improvement in the circulation has also been reported by tourniquets applied to the lower extremities. In both instances, the heart muscle for a brief period of several hours is allowed to function on a smaller volume of blood and its recuperative power under these circumstances is at times startling. We feel justified in broaching the proposition that positive pressure respiration, properly controlled, may diminish the volume of blood the heart has to deal with and, therefore, constitute a beneficial rather than an adverse influence. Studies with this in mind are contemplated, namely, the effect of more continuous but somewhat milder degrees of positive pressure administered continuously during inspiration and expiration to patients with various forms of heart failure. We have outlined the discussion at this time, since it may account in part for some of the improvement observed in treating patients with pulmonary edema, to be described in the following section.

THE CLINICAL USE OF POSITIVE PRESSURE RESPIRATION IN ACUTE PULMONARY EDEMA

The technic of applying positive pressure continuously throughout the respiratory cycle has been described in detail in connection with helium-

oxygen therapy^{26, 30} The method consists of the provision of a closed circuit apparatus in which the ventilation and pressure are achieved by a motor blower unit capable of maintaining a pressure as high as 10 cm of water. In the earlier cases, a mouthpiece or mask was used to connect the patient with the apparatus. Later a hood was employed which made closure at the neck, modelled after the Benedict helmet metabolism apparatus. We shall present eight case histories which illustrate the clinical use of this therapeutic procedure.

CASE REPORTS

Case 1 A female, aged 54 years, had suffered from nervousness, weakness and heart pounding for four and a half years, on examination she was found to have a toxic adenoma. The basal metabolic rate was plus 27 per cent. The heart was moderately enlarged, blood pressure 200 systolic and 100 diastolic. The heart rate was 140. After iodine administration and rest in bed, she improved and thyroidectomy was performed. The day after operation she showed signs of advanced cardio-respiratory failure and became intensely dyspneic and cyanotic. Supra-sternal retraction was evident during inspiration. The pulse rate was rapid, 140, thready volume and soft. Blood pressure dropped to 80 systolic and 60 diastolic and returned to 120 systolic and 80 diastolic. The venous pressure climbed to 280 mm. Moist râles were heard throughout both lungs and audible gurgling appeared in her throat. Her head moved backward with each inspiration. Respiration was extremely shallow and rapid, rate 50. She appeared moribund.

She was treated with inhalation of 50 per cent helium and 50 per cent oxygen under a pressure of 7 cm of water, lowered later to 5 cm. Within 15 minutes, the signs of pulmonary edema had disappeared. There were no gurgling noises, the moist râles were no longer audible. Improvement continued. She became conscious and five hours later breathing was deep and easy, the lungs were clear, cyanosis was greatly lessened. The pulse was of good volume, rate 120, blood pressure 160 systolic and 120 diastolic. Venous pressure was 125 mm.

The patient's temperature, however, continued to rise. When the mouthpiece rebreathing apparatus was removed for one minute, the signs of edema began to reappear. During the night she showed returning circulatory failure, pulse rate 160, venous pressure 250 mm, blood pressure 190 systolic and 100 diastolic, dropping later to 130/? Temperature was 107° F. She died the following morning. Before death, no râles could be heard over the front of her chest.

A thyroid crisis associated with circulatory failure was the apparent cause of death. The earlier clinical improvement as a result of the application of positive pressure was striking. Helium was added to oxygen because the marked supra-sternal retraction suggested some degree of obstruction of the respiratory passages. The rapid disappearance of edema was distinctly due to the administration of pressure, as it recurred almost immediately after withdrawal of positive pressure. The cause of edema seemed to be mainly the result of left ventricular failure.

Case 2 A male, aged 50 years, developed acute bronchopneumonia following hemorrhage from a tuberculous lesion. On the fourth day, acute pulmonary edema, together with signs of cardiac failure, was manifest. The pulse became rapid, 150, thin and thready, and the liver was palpable two fingers below the costal margin. A mixture of 50 per cent helium and 50 per cent oxygen was given under 5 cm pressure. Physical examination of his chest one hour later revealed absence of all moisture in the lungs. Twelve hours later, the pulse was 100, respiratory rate was 24, and he was comfortable. The rebreathing pressure apparatus was removed without recurrence of edema. However, the patient's temperature rose abruptly with

a spread of the bronchopneumonic process, but without pulmonary edema. He died 24 hours later.

The cause of pulmonary edema was thought to be due to the joint influence of left ventricular failure and increase in capillary permeability associated with inflammation of the lung and anoxemia.

Case 3 Male, aged 62 years. *History* The patient's mother had asthma and he himself suffered from hay fever for six years. Asthma began three years before admission, relieved by adrenalin. Patient entered the hospital in a state of severe status asthmaticus unrelieved by three injections of adrenalin, 1 cc each, and an injection of morphine, gr $\frac{1}{4}$ during a five hour period. He was in a generalized spastic state with marked carpopedal spasm. Inspiratory dyspnea was extremely severe and the patient suddenly stopped breathing. After injection of 1 cc of adrenalin he began breathing again but with extreme difficulty. The respiratory rate decreased progressively to two per minute. Blood pressure dropped from 170 systolic and 110 diastolic to 110 systolic and 70 diastolic. He developed edema of the lungs and frothy fluid came into his mouth. He was pale, eyes were rolled back and his jaws clamped. The pupils did not react to light. Inspiration was short, respiration prolonged with a high-pitched sibilant whistle. The pulse was at first fast and irregular and later imperceptible. Fifty cc of 50 per cent glucose intravenously had been administered without noticeable effect. He was then put in the hood helium apparatus with 21 per cent oxygen and 79 per cent helium and 5 cm water pressure. Breathing increased in depth and rate and the pulse became palpable. He was given 10 cc of calcium gluconate and 20 cc of dilute hydrochloric acid (1-1,000) intravenously without effect on the marked spasm. Metrazol was injected subcutaneously in 4 cc doses at two hour intervals for three doses. The breathing progressively improved and 12 hours later he was out of danger with slight asthma persisting. The signs of edema disappeared within the first hour of the treatment. On the following day helium was discontinued and the day after the patient was free from asthma. He left the hospital without asthma, one week later.

In this patient edema of the lungs appeared to develop as a result of

1 A previously existing pathologically elevated negative pressure due to inspiratory dyspnea, which exerted a suction action on the pulmonary capillaries

2 Fatigue and imminent paralysis of the respiratory center (To be discussed in case 7)

3 Left ventricular failure

The rapid pulse with marked decrease in volume which patients with asthma develop appears to be due to the high negative pressure existing within the chest which facilitates the entrance of blood into the right side of the heart and into the lungs but retards the passage of blood from the chest into the aorta. It may be generally observed that the volume of the pulse is either markedly diminished or becomes imperceptible at the end of the inspiratory cycle when the negative pressure within the chest is at its height. During expiration the pulse returns and increases in volume. The blood pressure frequently drops below the point of determination at the end of inspiration. It seems, therefore, likely that in this patient passive pulmonary congestion was present due to the failure of the left ventricle to discharge the customary volume of blood.

Case 4 A female, aged 37 years, became acutely ill two days after onset of a coryza, with the development two days later of signs of consolidation in the right upper lobe. She showed progressive pulmonary involvement, with high fever and marked toxicity. All lobes showed consolidation except the left lower lobe. The sputum and blood contained pneumococcus type V. Treatment with positive pressure, 5 to 7 cm water, and 100 per cent oxygen was applied when exitus seemed

momentarily imminent. She was comatose and deeply cyanotic. Respiration was very labored with moist râles heard extensively over the anterior portion of the chest and in the throat. Retraction was present in the supraclavicular fossa. Pulse was very thin, rate 150. Blood pressure had dropped from 160 systolic and 85 diastolic to 110 systolic and 50 diastolic.

Within 15 minutes after initiation of positive pressure, all signs of edema cleared. She breathed more deeply, with less supra-sternal retraction and labor. Cyanosis was markedly diminished and pulse rate and volume improved. No decline in fever or toxicity occurred, and she died 48 hours later, temperature 106.2°. The signs of edema continued to be absent as long as positive pressure was maintained, but returned when the apparatus was removed. The cause of the pulmonary edema was thought to be increased capillary permeability due to inflammation and anoxemia, with left ventricular failure as a contributory cause.

Case 5 A male, 72 years, showed a rising temperature the day after a second stage supra-pubic prostatectomy. On the fourth day his temperature was 104.6°, pulse 120, thin and soft, respirations 40. He became comatose, moist râles appeared throughout the lungs, and he appeared moribund. The clinical diagnosis was bronchopneumonia, edema of the lungs, cardiac insufficiency. He was treated with 100 per cent oxygen under a pressure of 5 cm. of water, using a mouthpiece rebreathing apparatus. The signs of edema were markedly decreased within 15 minutes, the pulse rate decreased from 120 to 108, his breathing was deeper, and moderate cyanosis previously present was much lessened. His lungs did not again show outspoken edema. However, his pulse weakened and on the following morning, 20 hours after the onset of positive pressure, he died, death being due to cardiac failure. The cause of pulmonary edema was thought to be left ventricular failure with an increased capillary permeability due to pneumonia.

Case 6 Female, aged 26 years. History. The patient had pneumonia two months previously. She now entered the hospital with fever, dyspnea and a pain in her chest for four days. A rising temperature and pulse continued for three days and she appeared extremely ill with severe dyspnea accompanied by neck muscle retraction on inspiration and a moderate degree of cyanosis in an oxygen tent with 50 per cent oxygen concentration. The respiratory rate was 40. Examination of the lungs revealed fine crackling (crepitant) râles over the right upper lung and the left upper lung and left axilla, with many moist râles over the anterior and axillary regions on the left side. Over the heart presystolic and systolic murmurs were heard at the apex. The pulse was 120 and small in volume. White blood cells 20,600, polynuclears 86 per cent. Sputum culture revealed Friedlander's bacillus.

The patient was treated with 100 per cent oxygen under a positive pressure of 3 cm. of water. After 15 minutes there appeared to be a definite although not marked diminution in the number of moist râles over the left anterior chest. However, there was no change in the number or character of the fine sticky râles. One hour later there seemed to be a slight further lessening of the number of moist râles. On the following day the patient was improved. There was a smaller number of both fine and medium moist râles over the chest. She was treated for one hour with 100 per cent oxygen under a positive pressure varying from 3 to 5 cm. of water. There was no definite change in the râles in the chest. The patient appeared completely comfortable in the hood on both occasions. The dyspnea was less marked and there was a distinct lessening of the retraction of the neck muscles during inspiration.

No consistent changes were observed in either the systolic or diastolic blood pressure, the pulse and respiratory rates. No change in the venous pressure could be attributed to breathing against 3 cm. positive pressure but when 5 cm. was employed there was a consistent but very slight increase of the venous pressure, ap

proximately 10 mm of water. This degree of elevation of the venous pressure is extremely little when compared to the effect of positive respiration on patients with congestive heart failure, and indicates that the patient was able to compensate in some way for the resistance interposed to the flow of blood into the right heart. In fact, normal subjects generally showed a rise of 20 mm of water, this may be due to the increased blood flow associated with the pneumonia.

The patient gradually improved and recovered. The case is presented primarily to indicate that positive pressure respiration of the degree employed does not result in a disappearance of râles which are presumably of an inflammatory etiology. There was no change in the fine sticky râles although there was a slight but definite diminution of the larger moist râles over the front of the left chest. The function of positive pressure in causing a more marked relief of dyspnea was clearly revealed. The inspiratory neck muscle retraction gave evidence that the widely consolidated lung was moved only by a markedly increased inspiratory effort. This was plainly alleviated by the inhalation of oxygen under positive pressure. It was also of interest that no significant changes occurred in the circulation except the extremely slight elevation in venous pressure noted above. Although the large and medium-sized moist râles appeared to indicate the beginning of pulmonary edema it is impossible to state that the short period of treatment given the patient had anything to do with the outcome. The case is presented not as a therapeutic result but to indicate the limitations of positive pressure respiration in checking or in removing inflammatory exudate, in the same time interval in which a transudate of edema fluid can be abolished. It is not possible to say what a longer period of treatment would have accomplished but it is of interest that the patient was more comfortable under positive pressure respiration than she was in atmospheric oxygen.

Case 7 Male, aged 59 years. History. Following an attack of bronchopneumonia, which seemed to clear, the patient developed asthmatic breathing, a harassing cough, and mucopurulent expectoration. The asthmatic breathing, though varying in intensity, became progressively worse in the succeeding two months, and was unrelieved by adrenalin, rest in bed, or oxygen. There were apparently no contributory factors in the past history. He was removed to the hospital in acute distress, breathing with severe difficulty, with markedly prolonged expiration. Sibilant râles were heard throughout the chest. Moderate relief was obtained by two treatments of helium and oxygen under 4 cm positive pressure. He was put into an oxygen tent, oxygen concentration 50 per cent, for the night with the idea of resuming helium therapy in the morning. Three doses of morphine, grains $\frac{1}{4}$ each, were given during the night, the last administered without the knowledge of the attending physician. When he was seen in the morning his condition appeared moribund. He was a large well-developed man, cyanotic even in 50 per cent oxygen. Respiratory rate had declined to 2 to 4 times a minute. The breathing took place as a short gasp, accompanied by a loud mucous gurgling which emanated from his throat and partially obscured the moist and sibilant râles heard on auscultation over the front of the chest. His pulse was full and bounding, rate 90, apparently an asphyxial pulse. He had been given 50 cc of 50 per cent glucose intravenously without noticeable relief. In the presence of what appeared to be imminent asphyxia due to respiratory failure he was given 21 per cent oxygen and 79 per cent helium under 5 cm positive pressure, at first through a mouthpiece and later through a mask closed-circuit apparatus. Within 10 minutes signs of pulmonary edema had cleared and auscultation of the chest showed that both lungs were being ventilated, accompanied by sibilant râles in inspiration and expiration. The respiratory rate had increased to 16. He was given 4 cc of metrazol and 20 grains of caffeine sodium benzoate in divided doses during the first half hour. The patient progressively improved and in an hour and a half opened his eyes and was partly conscious. His pulse was rapid, rate 136, but of

fair quality. He was kept on the helium-oxygen mixture for three days, the pressure being gradually lowered from 5 to 2 cm of water. At the end of that time the patient was in generally good condition. Although a moderate amount of asthmatic breathing continued, his pulse declined to 86 and he was eating three good meals a day.

On two subsequent occasions the patient developed severe obstructive dyspnea which required helium treatment for a period of a week almost continuously, with intermittent inhalations of helium with oxygen at intervals following the continuous treatment. He was treated with autogenous and stock vaccines, potassium iodide and roentgen-ray therapy. Two bronchoscopies were performed which revealed unusually small bronchi, their diameter comparable to that expected in an older child. After a series of reversals the patient seemed on the road to recovery, although at no time was his chest free from sibilant râles. For a period of one month, however, he seemed in such good condition as to be allowed up in a chair and to do a small amount of walking. A graphic record of his tidal air showed expiration to occupy 69.9 per cent of the respiratory cycle, whereas three months before it was 86.7 per cent. It is noteworthy that at no time did injection of adrenalin clear the râles in his chest, although improvement was often noted following its use, and some improvement following the inhalation of a 1-100 adrenalin spray. The patient had planned to leave the hospital in one week, when a return of severe difficult breathing took place, apparently associated with increased activity. His condition became progressively worse, and finally gasping respiration necessitated the use of helium and oxygen with a positive pressure of 5 cm of water. This gave him a moderate degree of relief, and it was thought that the condition would yield to treatment as it had three times in the past. However, each time the hood was removed, the patient was plunged into severe uncontrollable obstructive dyspnea. The patient died one week later of respiratory failure.

The diagnosis of this patient was (1) obliterative bronchitis and bronchiolitis of infectious origin, (2) edema of the lungs (the morning after admission to the hospital).

There was evidently not only an unusual narrowing of the main bronchi, but also a progressive intimal thickening of the bronchioles as well. The patient was in the hospital six months. It was believed that in the next to the last week of illness helium-oxygen therapy was postponed for a period sufficient to cause a marked increase in edema of the walls of the smaller bronchi and bronchioles due to the persisting pathologically elevated negative pressure within the chest.

The patient's reaction to helium-oxygen treatment under 5 cm water pressure the morning after admission could be attributed mainly to the maintenance of the positive pressure, which appeared to result in a swift disappearance of pulmonary edema, the restoration of pulmonary reflexes and return of activity of the respiratory center. The function of helium was undoubtedly to allow a deeper penetration of the mixture of 21 per cent oxygen and 79 per cent helium, but this could not have been achieved unless the edema had first cleared.

The cause of the initial pulmonary edema was considered due to (1) the previous presence of a high intrathoracic negative pressure resulting from inspiratory dyspnea, (2) the administration of excessive doses of morphine. By depressing the respiratory center, the respiratory rate was not only markedly decreased but there was a diminution in expiratory effort. The patient with asthma, by maintaining a prolonged expiration against a constricted orifice, develops an increased positive pressure between the site of obstruction and the alveolar capillaries. The abrupt termination of this pressure, by decreasing the intensity and rate of respiration, is followed by an increase in permeability of the capillary wall, as will be more fully discussed later.

Case 8 Male, aged 50 years. History. Patient entered hospital complaining of

epigastric distress, an aching pain in the lower left chest of six months' duration. He had a productive cough with blood streaked sputum and during this period lost 22 pounds. When he was admitted to the hospital, examination of the chest showed bronchial breathing and dullness over the left lower lobe. The brachial arteries were palpable, blood pressure was 130 systolic and 75 diastolic. As a result of bronchoscopy and biopsy, a diagnosis of carcinoma of the left bronchus with involvement of the lung, atelectasis and pleural effusion was made. Following a finger infection, for which he was given prontosil, he developed bronchopneumonia on the ward with widespread consolidation, and, two days later, edema of the lungs. He became deeply cyanotic, a loud gurgling was heard in his throat and moist râles over the chest. His pulse was 136 and of small volume, respiratory rate 40, temperature 103°. The administration of 50 per cent oxygen in an oxygen tent only slightly relieved the marked cyanosis. Positive pressure respiration was used with 100 per cent oxygen under 6 cm water pressure and within one hour the patient was much improved, there was no gurgling to be heard in the throat and many but not all of the moist râles had cleared. His color was markedly improved. A roentgen-ray of the chest showed a tremendous amount of irregular consolidation and metastases as well as marked cardiac enlargement. One hour after positive pressure respiration, a repeat roentgen-ray of the chest at the same distance showed the heart shadow was decreased 1.5 cm in its transverse diameter, and a marked increase had occurred in the radiability of both lung fields. The breathing continued to be shallow and the patient failed to make a further improvement. Twenty-one hours later respiration became slower and more shallow and the patient died of respiratory failure. A few moist râles were still heard over the chest but there was no recurrence of the widespread edema present before treatment. The cause of edema in his case seemed more closely related to the factor of increased permeability due to inflammation and anoxemia, perhaps accentuated by prontosil. Left ventricular failure may have been a secondary contributory factor.

DISCUSSION

The cases that have just been reviewed indicate that positive pressure respiration may be used as an effective therapeutic procedure in acute edema of the lungs. The primary illness in which pulmonary edema occurs as a complication is frequently of such severity that an ultimate recovery cannot always be expected. However, there are cases as moribund as occurred in this series in which a clearance of pulmonary edema allows the patient opportunity to recover from the primary illness.

The pathogenesis of acute edema of the lungs is a varied one. The factors involved may be listed as follows: 1. Left ventricular failure. 2. Increased permeability of the pulmonary capillaries. 3. (a) A persisting pathologically elevated negative pressure within the chest, or (b) an abrupt termination of expiratory effort and a consequent loss of the backward pressure on the pulmonary capillaries. In case 1 the essential factor appeared to be left ventricular failure. Right ventricular failure was also present. Following removal of the thyroid gland the patient developed a thyroid crisis which was the exciting cause of cardiac failure the day after operation. The pulse became extremely rapid and in small volume. The blood pressure dropped to as low as 80 systolic and 60 diastolic, the venous pressure climbed to 280 mm of water. Moist râles appeared in both lungs and gurgling was heard from the throat. It would seem likely that failure

of the left ventricle was responsible for backing up of blood in the lungs, increased hydrostatic pressure outward from the distended capillaries and finally exudation of serum. Since some anoxemia and capillary distention were also present, an additional factor may have been increased permeability of the lung. The marked elevation in venous pressure indicated an associated failure of the right ventricle. The swift clearance of pulmonary edema following the administration of a pressure of 7 cm of water exerted a direct opposing force on the pulmonary capillaries, counteracting their tendency to ooze serum. The effect of positive pressure within the chest was also to retard the entrance of blood into the right heart and relieve the left ventricle as well as the right. As a result breathing became deep and easy, the lungs were clear and the circulation markedly improved. The venous pressure fell to 125 mm. In this instance, there was for a temporary period not only a clearance of pulmonary edema but a restoration of some degree of function of both the left and right ventricle.

In case 5 a man 72 years old on the fourth day following a prostatectomy developed broncho-pneumonia associated with cardiac insufficiency and edema of the lungs. In this case there were probably two factors at work, left ventricular failure and an increased capillary permeability due to pneumonic inflammation, anoxemia and capillary distention.

Case 4 was a woman of 37 years of age who suffered from massive consolidation of both lungs due to pneumococcus type 5. There was a blood stream infection with the same organism. Development of edema in her case seemed to be associated with increased capillary permeability due to inflammation and anoxemia. The fact that the pulse volume was extremely small with a rate of 150 and that the blood pressure dropped from 160 systolic and 85 diastolic to 110 systolic and 50 diastolic suggested that left ventricular failure was a contributory cause.

In case 2 a man of 50 years developed acute broncho-pneumonia following a hemorrhage from tuberculous lesion. On the fourth day, acute pulmonary edema developed accompanied by the signs of heart failure. The pulse mounted to 150 and was of small volume. The liver was palpable two fingers below the costal margin. In this case, left ventricular failure appeared to be the precipitating cause with increased permeability, due to inflammation and anoxemia, as the contributing factor. The clearance of pulmonary edema, the fall in pulse rate to 100 and the disappearance of other signs of cardiac failure, which took place in this patient, indicated that positive pressure respiration exerted its effect both as a physical force opposing a further tendency of the capillaries to ooze serum and as a restoration of cardiac function by limiting the volume of blood handled by the heart. The fact that 12 hours later pressure could be removed without recurrence of edema was added evidence that the essential cause of the edema was left ventricular failure.

The cases that have just been reviewed have some similarity to the experimental production of pulmonary edema following intravenous injec-

tion of adrenalin In this type of edema our experimental evidence suggests that retarding the flow of blood into the right heart, thus enabling the heart to deal with a smaller volume, is of value in helping it to regain its function The action of positive pressure in this respect is comparable to tourniqueting the extremities which is a therapeutic procedure of value in pulmonary edema

In case 8, a man with widespread carcinoma of the lungs who developed broncho-pneumonia, the onset of edema of the lungs appeared to be associated with an increased permeability of the pulmonary capillaries as the most likely essential factor, with left ventricular failure as a contributing cause One hour after positive pressure respiration was begun roentgen-rays showed a marked increase in radiability of both lung fields and a decrease in the transverse diameter of the heart of 1.5 cm In his case not all of the moist râles in the lungs disappeared but the clinical improvement was at first quite marked In case 6, a young woman with pneumonia due to the Friedlander bacillus, positive respiration was followed by a diminution of the loud moist râles over the anterior chest but not by any change in the crepitating râles In another patient (whose case history is not reported in this paper), a clinical diagnosis of acute pulmonary edema following broncho-pneumonia was not confirmed by autopsy A woman of 54 years of age was ill for seven days with fever, cough and dyspnea On physical examination, scattered moist râles were present over both chests from the onset of illness She had long-standing mitral valvular disease with enlarged heart On the seventh day of disease, severe dyspnea developed, accompanied by loud moist râles over the anterior chest and gurgling noises emanating from the throat After three hours of positive respiration, 60 cm positive pressure being employed in the hood, the right anterior chest was free from râles during inspiration, although loud moist râles could still be heard over the left anterior chest There was an initial clinical improvement during the first eight hours of treatment which was followed by a progressive weakening of the patient and death 12 hours later At autopsy, no pulmonary edema was found, the bronchi were filled with purulent exudate The moist râles evidently had their origin in the bronchi and were apparently due to inflammatory exudate and not a serous transudation Although the inspiratory dyspnea was relieved by distention of the lungs from without, there was only a partial clearing of the widespread signs of moisture

The effectiveness of positive respiration seems more pronounced in the cases in which serous oozing is present and less noticeable in those in which inflammatory exudate is the cause of the râles in the chest In the majority of cases of pneumonia, the onset of pulmonary edema is not accompanied by a prolonged circulation time, according to King and his collaborators,²⁸ which would suggest that pulmonary congestion due to heart failure is not the precipitating cause of the condition However, more cases of pulmonary edema in pneumonia will have to be studied before the value of this treat-

ment can be determined. The most convincing and dramatic response to positive pressure respiration has occurred in those patients in whom some degree of failure of the left heart seemed clinically evident. In cases 3 and 7, the cause of pulmonary edema appeared to be different from that in the group just discussed. A predisposing factor seemed to be the previous presence of a high negative pressure within the chest due to severe inspiratory dyspnea, which may be compared to the development of pulmonary edema in animals subjected to respiration against a narrow orifice or against negative pressure.

In the discussion on the experimental production of edema that occurred after tracheal stenosis it was shown that the intrapleural negative pressure might increase to 10 times the normal value and that the heightened negative pressure exerted a suction action on the pulmonary capillaries. The same influence aided the inflow of blood into the right heart and hindered the exit of blood from the chest into the extra-thoracic aorta, thus, the factor of pulmonary congestion was added. In severe asthma the same mechanical influence takes place. The senior author has on one occasion demonstrated a markedly elevated negative pressure (-17 cm of water) in a case of severe asthma.

There is another important factor in the development of pulmonary edema in the two cases now being discussed. In each of them it will be remembered that the respiration rate decreased to two per minute. In case 7, three doses of morphine were given during the night. By depressing the respiratory center, the respiratory rate was not only markedly decreased but there was a marked diminution in the force of respiration. The ventilation of the lungs was, therefore, markedly diminished with the result that severe anoxemia was present, which is itself a factor in increasing capillary permeability. There is, however, still another factor that seems to be significant, namely, a sudden loss of a previously existing positive pressure against the pulmonary capillaries due to the patient's own expiratory efforts. The prolonged expiration of the patient with asthma results in an increased positive pressure between the site of bronchial constriction and alveolar capillaries. When this high positive pressure is abruptly terminated, the pulmonary capillaries become immediately more permeable.

It has long been known that in patients in whom laryngeal obstruction has existed for a considerable period, the provision of an unrestricted airway by tracheotomy is regularly followed by an outpouring of edema fluid from the lungs and bronchi into the trachea, which requires aspiration and suction at half hour to one hour intervals for many days and sometimes weeks. Woodman²⁹ showed that when the patient, immediately after tracheotomy, was made to exhale under a positive pressure comparable to that present prior to the relief of the obstruction that edema fluid would not collect in the trachea. Kernan and Barach³⁰ treated three patients who began to show this characteristic filling of trachea and bronchi with edema fluid by the application of positive pressure during the expiratory cycle. The pres-

sure at the beginning of treatment was 7 cm of water. This was gradually lowered during a two day period when the pressure was removed without any recurrence of edema fluid in the trachea. In one of these patients who had carcinoma of the lung there was the additional complication of hemorrhage. In this case after three hours of respiration against positive pressure there was not only an absence of edema fluid but the bleeding had stopped. This suggests that positive pressure may be used for cases of hemorrhage from the lung of capillary or venous origin.

There is, therefore, definite evidence that the sudden removal of a previously existing backward pressure on the pulmonary capillaries is followed by an increased permeability of the capillary wall and that the reestablishment of this positive pressure comparable to what the patient had become accustomed to stops the leakage of serum. In patients with asthma the use of morphine in doses which markedly diminish the respiratory effort has, therefore, the danger of precipitating edema of the lungs. The sudden development of pulmonary edema after aspiration of pleural effusion may be due at least in part to sudden removal of a relative positive pressure and exposure of certain lung alveoli to resumption of negative pressure.

The senior author has already suggested that the expiratory grunt in lobar pneumonia has the physiological advantage of maintaining increased positive pressure against the alveolar capillaries at the beginning of expiration. That this grunting respiration is not simply a subjective complaint on the part of the patient but has the functional significance of preventing pulmonary edema was suggested by the observation of a case of lobar pneumonia that developed acute edema of the lungs following the administration of $\frac{1}{2}$ gram of morphine. The patient had extensive involvement of both lungs due to pneumococcus type 3. He was in marked dyspnea and emitted a loud grunt at the start of expiration. After the administration of morphine the patient's respiration became shallow and slow without any grunt. He went to sleep and one hour afterwards had generalized edema of the lungs.

It has also been pointed out that patients with emphysema frequently partially close their lips during expiration and find that their breathing is made easier than when the mouth is open. We have made use of this observation in the treatment of patients with chronic asthma of moderate degree suggesting to the patient that he arbitrarily increase the resistance to the egress of air during expiration. In many instances a therapeutic exercise of this character pursued for three to five minutes will terminate an attack of wheezing, indicating that this backward distending pressure on the bronchioles tends to keep them patent. Certain areas of the lungs may have become accessible to ventilation, which previously were shut off by collapsed ducts or thin webs of mucus.

We do not mean to condemn completely the use of morphine for asthma or pneumonia since a moderate decrease in pulmonary ventilation relieves inspiratory dyspnea and lowers the negative intrapleural pressure. Doses

which exert a markedly depressive influence on the respiratory center have, however, the dangers which we have just described. It is of interest in this connection that Prickman³¹ has also reported a case of asthma that became moribund after the administration of morphine and that finally recovered with the inhalation of helium and oxygen.

Although we have no clinical or experimental observations on the production of acute pulmonary edema through irritant gases it may be pointed out that the earliest case on record in which positive pressure respiration was used was in a patient who developed edema of the lungs following ingestion and inhalation of carbolic acid. In this remarkable report there was a clearance of edema after an hour's treatment.⁵ This manifestly suggests its use in the treatment of pulmonary edema caused by irritant gases such as chlorine in commercial use and phosgene and other gases employed in war gas poisoning. This type of edema can be ascribed to increased permeability of the capillary wall due to irritation and inflammation.

SUMMARY

Acute pulmonary edema has been studied from an experimental and clinical point of view. Three pathogenetic factors have been discussed.

- 1 Alterations in the pressure within the lung
 - a A prolonged pathologically elevated negative chest pressure
 - b An abrupt termination of backward pressure against the pulmonary capillaries
- 2 Left ventricular failure
- 3 Increased permeability of the capillary walls

Following the production of tracheal stenosis it has been shown that edema of the lungs takes place associated with a marked elevation in intrapleural negative pressure. The pathological physiology thus produced exerts a two-fold influence.

- a A direct suction action on the pulmonary capillaries increasing the tendency to ooze serum through their walls

- b A promotion of the inlet of blood into the right heart and a retardation of the flow of blood from the chest into the extrathoracic aorta, factors which increase pulmonary congestion. These physiological events are comparable to what takes place clinically in asthma and dyspnea due to obstructive lesions in the respiratory tubal passages.

As a result of large doses of morphine respiratory effort may be abruptly diminished. Although this makes for a reduction of the intrapleural negative pressure during inspiration, it also takes away the backward pressure which has been previously exerted against the capillaries lining the alveolar walls, as the patient attempts to deliver air through narrow bronchi and bronchioles. Expiration is proportionately much longer than inspiration and the removal of this accustomed back pressure has been found to result in pulmonary edema. Similarly, the removal of long standing obstruction

of the larynx by tracheotomy has been shown to result in an oozing of sero-mucous fluid. The application of positive pressure restores the accustomed backwardly directed pressure and prevents further oozing of serum from the capillary walls.

The experimental production of pulmonary edema in rabbits after intravenous injection of adrenalin has been shown to be due mainly to a left ventricular failure. Under these circumstances no elevation of the negative pressure within the intrapleural cavity was found. It was shown that the left heart was contracted, that the right heart was dilated, disproportion between the output of the two ventricles was, therefore, assumed. A marked passive congestion takes place in these animals followed first by passage of red corpuscles and later serum into the alveolar cells. An increased hydrostatic pressure in the pulmonary capillaries may be assumed under these circumstances to be the main factor, contributory factors being increased capillary permeability due to anoxemia and distention of the capillary walls. This type of experimental pulmonary edema appears to be comparable to that which follows left ventricular failure in clinical disease.

Concerning the third factor, there is evidence that anoxemia, inflammation, and distention of the walls of the capillaries increase capillary permeability. In cases exposed to irritant gases it may be assumed that increase in capillary permeability due to irritation and inflammation is of predominant importance.

Physiological observations were made on the effect of positive pressure respiration on normal subjects, on patients with congestive heart failure and a miscellaneous group. It was shown that when respiration is conducted under a positive pressure of 6 cm. of water normal individuals show a slight elevation in venous pressure, approximately 20 mm. of water and a prolongation of the circulation time of approximately $3\frac{1}{2}$ seconds. In patients with congestive heart failure the venous pressure is increased, in some instances as much as 60 mm. of water and the circulation time may be prolonged 10 to 15 seconds. The heart under these circumstances deals with a smaller volume of blood, due to the fact that the positive pressure within the chest prevents the customary entrance of blood into the right auricle. Explanation of the difference between the behavior of normal subjects and persons with congestive heart failure was listed as follows:

- 1 The diminished elasticity of the congested lung prevents a compensating rise in negative pressure within the chest which is theoretically possible for the normal individual.

- 2 The positive pressure within the chest creates a greater interference with diastolic filling of the diseased heart, as compared to the normal.

The marked prolongation of circulation time found in some cardiac patients is not necessarily looked upon as a harmful influence since the decreased volume of blood with which the heart works may be helpful in restoring its function, despite the fact that greater back pressure is present in the systemic veins. Tourniquets applied to the extremities similarly

reduce the amount of blood entering the heart, a procedure which has been found of special value in treating edema of the lungs and "cardiac asthma"

The use of positive pressure respiration in 8 clinical cases of edema of the lungs is described. The effect of the procedure was in most instances a swift clearance of edema and a betterment of the state of circulation. The function of positive pressure in these cases, as in the experimental production of pulmonary edema, was to exert a direct opposing physical force on the external capillary wall tending to counteract the tendency to ooze serum and to decrease the inlet of blood into the right heart, in that way diminishing pulmonary congestion and permitting the heart to work on a smaller volume of blood. An attempt was made to discuss the importance of the factors which have been outlined in each individual case.

CONCLUSION

Acute pulmonary edema has been studied from an experimental and clinical point of view. In cases of respiratory obstruction the pathologically elevated negative pressure within the chest exerts a suction action on the pulmonary capillaries resulting in a tendency to ooze serum through their walls. Expiration against a constricted bronchial passageway maintains a backward pressure against the pulmonary capillary wall, inhibiting the leakage of edema fluid. A sudden termination of obstructive dyspnea, through excessive doses of morphine or as a consequence of tracheotomy, may be followed by edema fluid in the tracheo-bronchial tree. Positive pressure respiration has been found clinically helpful in the treatment of pulmonary edema associated with respiratory obstruction.

The pathogenesis of acute pulmonary edema arising as a complication of heart failure seems best explained by the original hypothesis of Welch. "A disproportion between the working power of the left ventricle and of the right ventricle of such character that the resistance being the same the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." Positive pressure decreases the amount of blood entering the right heart and in that way diminishes pulmonary congestion and facilitates the clearing of pulmonary edema. When the lungs are distended from without by positive pressure there are the additional effects (a) a lowering of the negative pressure within the chest during inspiration and (b) a direct opposing physical pressure on the pulmonary capillaries, especially during expiration.

When pulmonary edema is due to irritation and inflammation, resulting in an increased permeability of the pulmonary capillary walls, positive pressure respiration is at times less effective in clearing the signs of edema.

BIBLIOGRAPHY

- 1 WELCH, W. H. Zur Pathologie des Lungenödems, Virchow's Arch. f. path. Anat., 1878, LXXXII, 375.

- 2 MEITZER, S J Edema, a consideration of the physiologic and pathologic factors considered in its formation, *Am Med*, 1904, viii, 191
- 3 EMERSON, HAVEN Artificial respiration in the treatment of edema of the lungs, *Arch Int Med*, 1909, iii, 368
- 4 BARRINGER, T B Pulmonary edema treated by artificial respiration, *Arch Int Med*, 1909, iii, 368
- 5 NORTON, N R Forced respiration in a case of carbolic acid poison, *Med and Surg Rep Presbyterian Hosp*, N Y, 1896, i, 127
- 6 NORTHRUP, W P Apparatus for artificial forcible respiration, *Med and Surg Rep Presbyterian Hosp*, N Y, 1896, i, 127
- 7 OERTEL, M J *In* Von Ziemssen's Handbook of Therapeutics, Translated from the German by J B Yeo, Wm Wood & Co, 1885, iii, 547
- 8 AUER, J, and GATES, F L Experiments on the causation and amelioration of adrenalin pulmonary edema, *Jr Exper Med*, 1917, xxi, 201
- 9 JOHNSON, S The experimental production and prevention of acute edema of the lungs in rabbits, *Proc Soc Exper Biol and Med*, 1927-28, xlv, 181
- 10 GOLLA, F L, and SYMES, W L Reversible action of adrenalin and kindred drugs on the bronchioles, *Jr Pharm and Exper Therap*, 1913-14, v, 88
- 11 LOEB, LEO Mechanism in the development of pulmonary edema, *Proc Soc Exper Biol and Med*, 1928, xlv, 321
- 12 PLESCH, E P Funktionelle Gefassdiagnostik Beziehung zwischen Schlagvolumen und Gefasssystem, *Ztschr f klin Med*, 1933, cxliii, 208
- 13 POULTON, E P Left-sided heart failure with pulmonary edema treated with the pulmonary plus pressure machine, *Lancet*, 1936, ccxxxi, 983
- 14 MOORE, R L, and BINGER, C A L (a) Observations on resistance to the flow of blood to and from the lungs, *Jr Exper Med*, 1927, xlv, 655 (b) Response to respiratory resistance a comparison of the effects produced by partial obstruction in the inspiratory and expiratory phases of respiration, *Jr Exper Med*, 1927, xlv, 1065
- 15 (a) BARACH, A L Effects of inhalation of helium mixed with oxygen on the mechanics of respiration, *Jr Clin Invest*, 1936, xv, 47-61
(b) BARACH, A L The therapeutic use of helium, *Jr Am Med Assoc*, 1936, cvii, 1273-1279
- 16 TIGERSTEDT, N R *Ergebn d Physiol*, 1903, ii, 528
- 17 WIGGERS, C J Regulation of the pulmonary circulation, *Physiol Rev*, 1921, i, 239
- 18 DALY, I DE BURGH The resistance of the pulmonary vascular bed, *Jr Physiol*, 1930, lxi, 239
- 19 MOLLGAARD Fysiologisk Lungekirurgie, Copenhagen Quoted by Tigerstedt, *Physiologie des Kreislaufes*, 1923
- 20 HUGGETT, ST G Studies on the respiration and circulation of the cat—the heart output during respiratory obstruction, *Jr Physiol*, 1924-25, lxi, 373
- 21 LANDIS, E M Micro-injection studies of capillary permeability, *Am Jr Physiol*, 1927-28, lxxiii, 387
- 22 KROGH, A Anatomy and physiology of capillaries, 2nd Edition, 1929, New Haven
- 23 BARACH, A L The use of helium in the treatment of asthma and obstructive lesions of larynx and trachea, *ANN INT Med*, 1935, ix, 739 See reference 15
- 24 BARACH, A L, MARTIN, J, and ECKMAN, M Positive pressure respiration and its application to the treatment of acute pulmonary edema and respiratory obstruction, *Proc Am Soc Clin Invest*, 1937, xvi, 664
- 25 GRAHAM, E A Influence of respiratory movement on the formation of pleural exudates, *Jr Am Med Assoc*, 1921, lxxvi, 784
- 26 BARACH, A L Recent advances in inhalational therapy and treatment of cardiac and respiratory disease—principles and methods, *N Y State Jr Med*, 1937, xxxvii, 1095

- 27 CHRISTIE, R V, and MEAKINS, J C The intrapleural pressure in congestive heart failure and its clinical significance, Jr Clin Invest, 1934, xiii, 323
- 28 KING, F H, HITZIG, W M, BULLOWA, J G M (by invitation) and FISHBERG, A M The circulation in lobar pneumonia with special reference to pulmonary edema, Jr Clin Invest, 1936, xv, 452
- 29 WOODMAN, M On the control of air pressure in the lungs after tracheotomy, Jr Laryn and Otol, 1935, i, 214
- 30 KERNAN, J, and BARACH, A L To be published
- 31 PRICKMAN, L E The treatment of severe asthma, Proc Staff Meet Mayo Clinic, 1936, vi, 580

A SURVEY OF THE SO-CALLED HEMOLYTIC ANEMIAS

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INTRODUCTION

Pernicious Anemia and the Hemolytic Anemias Within the past few years, the problem of Addisonian pernicious anemia has been clarified by brilliant deductions and investigations until today, as a result, we have a satisfactory understanding not only of the mechanism of normal blood formation and of the several disturbances of this process which may lead to the same disease picture, but also of the method of action of the replacement therapy which acts so specifically and marvelously to save the lives of such patients. This is indeed a triumph to make us proud of those who accomplished this achievement.

During this same period, interest in the anemias which arise from increase in erythrocyte destruction has not been lacking, but unfortunately no corresponding progress has been made. Of course, something has been learned about individual forms such as hemolytic ictero-anemia and sickle cell anemia and a few additional forms of acute anemia from intense blood destruction have been identified. A little also has been learned of the process of hemolysis itself, of the relation of the reticulo-endothelial system to erythrocyte destruction and of the cycle of pigment metabolism, but there are still huge gaps in our knowledge of the fundamental process of erythrocyte destruction. From the clinical side we are still dealing with individual entities and we lack any better common basis for grouping these various anemias together under the term "hemolytic anemias" than a belief that they result from increased blood destruction although they may differ widely in the mechanism and location of that destruction.

It is true that we have learned a great deal about pernicious anemia, but it may be that even about that disease there is more to be discovered. One does not have to go very far back in memory to reach the days when pernicious anemia was defined as an hemolytic anemia with abnormal red cell formation, and I can well remember hearing discussions as to whether a patient with pernicious anemia exhibited sufficient evidence of hemolysis to justify the removal of the spleen. We all spoke glibly of the hemolytic and the aplastic types of pernicious anemia and we actually did seem to benefit some of the more hemolytic cases by splenectomy. I can recall several such patients and I wonder what they would today be diagnosed.

Undoubtedly there is an increased red cell destruction in pernicious anemia as is evidenced by the patient's yellow color, the increased urobilin output and the enlargement of the spleen. This increased hemolysis is

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thought to occur because the red cells which are produced by the pernicious anemia bone marrow are abnormal and are, therefore, more liable to destruction either by wear and tear, by phagocytosis or by true hemolysis. Nevertheless, we do not any longer include pernicious anemia among the hemolytic anemias, but it is interesting that the recent observations of Rhoads at the Rockefeller Institute tend again to place emphasis on the hemolytic aspect of this disease.

I have opened this survey of the hemolytic anemias with these remarks on pernicious anemia to point out the lack of clear separation between the various groups of anemias. It is, for this reason, that I used the term "so-called hemolytic anemias" in my title. We use the term pernicious anemia, dyshemopoietic anemia, deficiency anemia, aplastic anemia on the one hand and the term hemolytic anemia on the other—but we must remember that we are naming only what we believe to be the chief but possibly not the only factor in the pathogenesis of any one form. The separation between the two groups is not as distinct as we are apt to think. Inherently any disturbance of erythrocyte production will be reflected in erythrocyte destruction, any alteration in destruction will react on production. If the cells formed in the bone marrow are fragile, short-lived or liable to destruction by the normal red cell destroying mechanism of the body, then obviously increased hemolysis will occur with secondary hyperplasia of the blood destroying tissues, on the other hand, if abnormally rapid red cell destruction takes place, the bone marrow must, as long as it can, compensate by increased erythropoiesis and the cells put into circulation will surely be immature and may be below standard in other ways as well. And so a vicious circle tends to be established.

Each type of anemia will disturb both functions of what Krumbhaar named the "hemolytopoietic system." Furthermore, if it is the newly formed red cells which are destroyed and if this destruction occurs chiefly in the bone marrow by the cells of the reticulo-endothelial system, which as you know is distributed in the bone marrow as well as in the lymph nodes, liver and spleen, then the separation between disturbed production and increased destruction becomes even more difficult. One can arrive at a *reductio ad absurdum* if one wishes, by narrowing the problem down to whether the red cells die as it were *in utero* or are slaughtered by a sort of hemolytic Herod promptly after birth. It is the preponderance of the process, or the assumed initial fault which determines whether a given form of anemia is placed in one or the other group. Many remain in doubt. We are concerned at the time with those termed "hemolytic" and it is proper for us, therefore, to review our knowledge of the fate of the red blood cells in the body.

Normal Erythrocyte Destruction. Before proceeding to discuss the mechanisms of excessive destruction of red cells which lead to the various hemolytic anemias, we should consider the fate of the erythrocyte in the normal. Three methods of red cell destruction are recognized—phago-

cytosis by the cells of the reticulo-endothelial system, especially in the spleen, destruction by some hemolytic agent or condition of the plasma, and dissolution by simple wear and tear. Of these three methods, it is the third which in the normal would seem to be the physiologic fate of the red cells. Best¹ states that approximately one billion erythrocytes wear out every minute and must, of course, be replaced to keep the unit numbers of circulating red cells constant. Even in the normal there is some phagocytosis by the splenic cells and other cells of the reticulo-endothelial system but this is thought not to affect healthy erythrocytes. The spleen has been called the graveyard but not the slaughter house of the erythrocyte. Nothing is known as to the fate of the stroma and pigment of a red cell which happens to break up at a distance from the spleen and liver which are the chief collectors of reticulo-endothelial phagocytes, but reticulo-endothelial cells are present in all lymph nodes and in small numbers are widely scattered through the body.

It is said that, as a rule, hemolysis of erythrocytes in the strict meaning of the word does not occur in the normal, because there is no demonstrable hemoglobin in the normal blood plasma. However, this may be faulty reasoning based on tests not sufficiently delicate, for if erythrocytes break down at a distance from their graveyard, pigment must be liberated into the plasma. It is, of course, possible that local conditions, as for example in the spleen, may so alter the pH, the electrolyte pattern or the osmotic potentialities of the blood plasma as to predispose to the final breakdown there of aged or weakened corpuscles. One can assume, for example, that the blood returning from the stomach during acid secretion is altered in its reaction and in its electrolyte pattern. I have long been tempted to speculate on this point for the gastric vein which drains the stomach runs a curiously long course and eventually empties into the splenic vein or sometimes directly into the portal vein. If only this altered blood entered the spleen, the theory would be easy. For the present, however, we cannot go behind the accepted view that hemolysis does not occur in the normal. Of one thing we can be sure and that is that whatever the method of red cell destruction, the body carefully preserves for re-use the iron, the pigment and probably the other components of the erythrocytes, and that probably the stimulus to red cell production is to be found in the products of red cell disintegration.

Hemolysis and Hemolysins When we turn to consider hemolysis as it occurs in vitro and in vivo under a great variety of conditions, we find at once that we must not think of all hemolysis of erythrocytes as identical in mechanism, nor as a simple bursting of a liquid-containing cell with escape of its contents as the term hemolysis might seem to imply. It is important to remember that several methods of erythrocyte dissolution are included under this term hemolysis and that when one turns to the use of the term hemolytic anemia nothing more is implied than that the anemia results from increased erythrocyte destruction whether by phagocytosis or other means.

Perhaps it may not seem important in a consideration of the hemolytic

anemias for us to review the various methods by which different types of agents bring about destruction of erythrocytes, but it is important that we should not allow our familiarity with the action of hypotonic salt solution as a hemolytic agent to lead us to visualize all hemolytic processes as a simple matter of imbibition of fluid with a swelling of the cell and an assumption of a more and more spherical shape until rupture occurs. We suspect that that is the mechanism at work in certain hemolytic anemias but in others we feel sure that the method of destruction is far different and may or may not resemble one of the other methods which can be observed *in vitro*. For example, such chemical hemolysins as ether, chloroform, benzene and alcohol dissolve the envelope of the corpuscle and its stroma, bile salts and saponin also dissolve the stroma, acids act as does hypotonic salt solution and so do alkalis except that some also dissolve the stroma. Then there are the specific hemolysins such as are active in the hemolysis following a foreign blood transfusion and in the hemolytic system employed in the Wassermann test. Toxic substances without number may act as hemolysins including such widely differing agents as bacterial toxins, snake venom and even cold in susceptible persons who exhibit the Donath phenomenon. Even this list is far from complete and not all act similarly—for example, cobra venom acts by removing the unsaturated fatty acid from the lecithin molecule thus producing lyso-lecithin which is a violent hemolytic agent. When we come to consider the hemolytic anemias we must keep our minds open as to the methods by which the excessive red cell destruction may be caused. In some instances, it will be as obvious as in malaria, in others the weakness of the red cells apparently renders them easy victims to the normal destructive processes, in still others the presence of a known powerful toxin will seem to explain the pictures, but the process will not be the same in each nor will it be clear in all.

HEMOLYTIC ANEMIAS ACCORDING TO MECHANISM OF HEMOLYSIS

If we attempt to group the well-known forms of hemolytic anemia according to the pathogenesis of the increased red cell destruction, we find something like the following

TABLE I

- 1 Fault in the Erythrocyte
 - (a) Hemolytic ictero-anemia
 - (b) Sick cell anemia
 - (c) Hemolytic feature of pernicious anemia
- 2 Parasitic Destruction of Erythrocyte
 - (a) Malaria
 - (b) Oroya fever
- 3 Allergic Hemolysis
 - (a) Favism
 - (b) Occasional drug sensitivity Sulphanilamide, for example
- 4 Chemical Agents
 - (a) Exogenous—acetanilid, lead, snake venom
 - (b) Endogenous
 - 1 By bile salts in infants with jaundice?
 - 2 Altered plasma pH
 - (c) Conditioned—indol in dogs on deficient diet

- 5 Bacterial Toxin
 - (a) *B Welchii* infection
 - (b) Unidentified infection as in some cases of acute hemolytic anemia (Lederer)?
- 6 Mechanism Unknown and not Surely Hemolytic
 - Cooley's anemia
 - Erythroblastoses of infancy
 - Carcinomatosis??
- 7 Specific Hemolysins
 - Following transfusion of incompatible blood
- 8 Physical Agents Such as Cold
 - Paroxysmal hemoglobinuria
- 9 Excessive Destruction in Reticuloendothelial System
 - Reticulo-endotheliosis, Hodgkin's disease
- 10 Phagocytosis by Leukocytes
 - So-called "phagocytic anemia"

Obviously any such classification is open to criticism and no two persons would adopt exactly the same arrangement. Some of the groupings are fairly certain, others very uncertain. Everyone, I think, would agree in attributing the increased blood destruction of hemolytic ictero-anemia and of sickle cell anemia to the obvious abnormality of the red blood cells of patients with these conditions and this is probably correct. Yet it should be pointed out that although the red cells of ictero-anemia are fragile in hypotonic salt solution and habitually possess a spherical shape such as erythrocytes assume as they approach dissolution in hypotonic solution, we do not know where or how these so-called spherocytes meet their end in the circulating blood. Nor do we know what it is that brings about the sudden crises of hemolysis that characterize both ictero-anemia and sickle cell anemia. Sometimes even a slight intercurrent infection precipitates such a crisis of hemolysis and makes one wonder whether with the infection a bacterial toxin enters the blood and produces an added hemolytic action, or whether there occurs with the fever some change in the reaction or electrolyte pattern of the plasma, or merely a speeding up of the usual destructive function of the tissue phagocytes. It is a reasonable but unproved assumption that the increased red cell destruction of these diseases is wholly due to a weakness of the cells themselves. Such a weakness is demonstrable in ictero-anemia but not in sickle cell anemia, although the cells in both are obviously abnormal. To which is added the further assumption that the enlarged spleen of ictero-anemia with its great increase in reticulo-endothelial phagocytes is a secondary feature responding to the need of disposing of the enormous number of dying erythrocytes.

In malaria and Oroya fever, the mechanism of red cell destruction by the parasites appears obvious. If it is true, as has been reported in bird malaria, that the plasmodium attacks only youthful reticulated red cells, it is interesting to realize that the bone marrow's response to the blood destruction, floods the circulation with the very type of young cells on which the plasmodium thrives.

Favism appears to be the perfect example of allergic hemolysis—for the violent red cell destruction in this condition seems not to follow the first eat-

ing of the favus bean but only subsequent ingestions, or even inhalations of the odor of the plant. It would seem that a specific hemolysin must be elaborated in such individuals. The behavior of sulphanilamide in the occasional production of acute hemolytic anemia suggests at least that the factor of idiosyncrasy enters in in some cases. So perhaps this cause of hemolytic anemia should be classed as allergic rather than with the rest of the many exogenous chemical agents which quite regularly produce hemolysis. In this latter group, one may use acetanilid and lead as examples. The beautiful experimental work of Rhoads² and his collaborators has demonstrated that certain chemicals may cause hemolysis only when special conditions prevail—as for example, indol in dogs on a certain type of deficient diet—the indol apparently merely accelerating the action of other hemolysins (Ponder³).

Some very interesting studies by Ham⁴ in Minot's laboratory and by Dacie, Israels and Wilkinson⁵ in England, shed further light on the matter of hemolysis by changes in the chemistry of the blood. In some cases of chronic hemolytic anemia associated with paroxysmal nocturnal hemoglobinuria, a syndrome which has been named after its two Italian describers Marchiafava and Micheli, Ham was able to demonstrate that the nocturnal hemolysis was related to the elevation of the carbon dioxide content of the arterial blood and the associated decrease in the pH which occurs in sleep. Counteracting this shift with sodium bicarbonate reduced the hemoglobinuria, while ammonium chloride, as might be anticipated, increased the physiologic shift and the hemoglobinuria. This would seem to prove very prettily that the red cells of these patients are abnormally susceptible to hemolysis in plasma of increased acidity but within the physiologic range of pH variation. Unfortunately, alkali medication, while temporarily beneficial did not cure the condition and excessive blood destruction followed the omission of the sodium bicarbonate. An interesting review of some cases of this syndrome appeared recently in the *Quarterly Journal of Medicine*.⁶

Bacterial toxins such as that of the gas bacillus of Welch, undoubtedly cause hemolytic anemia in some infections, but there is much doubt and speculation as to how active in this respect other less virulent bacteria are. It is tempting but unjustified to attribute the anemia of many infections to a hypothetical hemolytic toxin. Similarly it is not known whether an infection is responsible for all or some of the instances of so-called acute hemolytic anemia of Lederer and others. Even less is known as to the cause and mechanism of Cooley's anemia and of the so-called erythroblastoses of infancy. Some deny the presence of hemolysis in these conditions but it seems to me that the picture is so like that of other known hemolytic anemias that we should accept them in our hemolytic group even if we do not know the agent or the method of increased erythrocyte destruction.

The remaining types of hemolysis need little discussion here. The mechanism of transfusion hemolysis is familiar to all of us, while hemolysis induced by cold usually in syphilitic subjects, the hemolytic anemia in Hodg-

kin's disease, and the occasional case of so-called phagocytic anemia are so rare as not to justify more than a passing mention

Again we are impressed with the variety of methods by which destruction of erythrocytes is occasioned and the great number of conditions in which some increased blood destruction occurs. Of course, the entire picture of hemolytic anemia does not appear in all of these patients, but potentially it might and at times does

Common Features of Hemolytic Anemia So far in this review we have been considering the mechanism which acts in the production of the increased red cell destruction which is the essential characteristic of any anemia which is to be classed as hemolytic. We must now pass on to some consideration of the clinical and laboratory phenomena which are common to this group of conditions, then to some of the manifestations peculiar to the more important individual entities and finally to the principles of treatment which apply to the hemolytic anemias in general

Although there are many mechanisms of increased blood destruction and many hemolytic anemias, there is a remarkable constancy in the manifestations common to the entire group. These fall naturally into three groups (1) the immediate evidences of the increased blood destruction, (2) the compensatory hyperplasia and hyperactivity of the reticulo-endothelial system and (3) the evidences of regenerative activity of the hemopoietic blood producing tissues

Of course, these phenomena will appear in different degrees and combinations in different varieties of hemolytic anemia, depending upon the severity and rapidity of the blood destruction, the duration of the process, the integrity of the blood forming tissues, et cetera. But by and large, every case of hemolytic anemia shows to some degree the same phenomena and so we may properly speak of the symptom complex of hemolytic anemia

Blood destruction liberates hemoglobin into the plasma in amounts proportionate to the number of erythrocytes destroyed. This pigment in amounts far in excess of that derived from normal degrees of blood destruction, tends to follow the normal course, being absorbed by the Kupffer cells of the liver and other cells of the reticulo-endothelial system to be excreted as bile, largely reabsorbed from the bowel, and re-utilized. However, the amount of reabsorbed pigment now in the form of urobilinogen is apt to be so great that some tinges the skin of the patient and some escapes through the kidneys in the urine. A yellowish facies and urobilin in the urine thus become common features of any hemolytic process of sufficient severity or chronicity, as was noted at the beginning of this paper, in discussing pernicious anemia. If the hemolysis is of still higher grade and the liberated hemoglobin reaches a figure of 0.7 gram per 100 cc of circulating blood, hemoglobin itself tends to pass the kidney filter and hemoglobinuria, another phenomenon common to many hemolytic processes, appears, as for example in black water fever and in the so-called Marchiafava-Micheli syndrome of nocturnal hemoglobinuria. It may be worth mention-

ing that from the point of view of these phenomena, there is little or no difference between an acute and primary attack of hemolysis with the rapid appearance of anemia, and an episode of increased blood destruction such as occurs in the course of a chronic hemolytic anemia, such as ictero-anemia or sickle cell anemia

The next feature common to hemolytic anemias is the hyperplasia of the reticulo-endothelial cells or to return to the usual simile of the graveyard—an enlargement of the cemetery. No doubt all the reticulo-endothelial system participates in this increased activity but we recognize it only in the enlargement of the spleen and perhaps the liver which occurs in almost every hemolytic process acute or chronic. The spleen is in man the largest mass of reticulo-endothelial cells and a demonstrable splenomegaly is accordingly expected in hemolytic anemias. Quickly before the question is asked, I must hasten to mention one important exception. The spleen is enlarged in sickle cell anemia only in the early stages and seems to go on to a reduced size as the disease progresses probably as a result of a fibrotic overgrowth, perhaps from irritation by phagocytized material.

Active regeneration of blood, or erythropoiesis, is another phenomenon characteristic of hemolytic anemia. This again varies greatly according to the rapidity of the blood destruction, the chronicity of the process, the condition of the bone marrow and indeed the age of the patient. In all instances, however, the changes in the blood picture are in the same direction—first occurs anemia or an increase in anemia, then after a variable time lag there appear immature red cells—erythroblasts and reticulocytes—and to some measure the anemia is halted or conquered. At the same time the number of white cells is increased by the appearance of more and more immature members of the marrow series—polymorphonuclears and myelocytes, probably due to the effect of active erythropoiesis on the adjoining leukopoietic centers in the marrow.

For many years, it has been assumed that the urobilin output and the evidences of regeneration in the blood bear some relationship in a rough way to the degree of blood destruction. Josephs⁷ at Johns Hopkins has been attempting recently to express these relationships in the form of an equilibrium. The many variables in the problem make this a very difficult matter. For example, any disturbance of blood production in either direction will confuse the picture as, for example, such an increase in red cell production as becomes established in hemolytic ictero-anemia or, on the other hand, such failure of bone marrow function as may eventually result. Josephs has also found it difficult to work out the balance when there is any great number of nucleated red cells—for while such erythroblasts are, of course, immature forms analogous to reticulated red cells, yet erythroblastosis may well be a deviation from normal red cell production and not merely a more active regeneration. As we will see when we come to discuss the individual hemolytic anemias, some exhibit more erythroblastosis than do others. It seems proper, however, to include both those that do exhibit marked

erythroblastosis and those in which blood regeneration is evidenced by the more usual reticulocytosis, together in the group of hemolytic anemias

Leukocytosis of cells of the marrow series, as has been mentioned, is a common feature of the blood picture of hemolytic anemia during the regenerative stage. This again is very variable and tends to be more marked in infants in whose blood there may appear not only a considerable number of youthful neutrophils—a shift to the left—but even myelocytes. It is important to remember this neutrophile leukocytosis of hemolytic episodes and avoid the error of using it as an argument in favor of an infectious basis for the hemolytic process in a given case.

There is still another feature of a number of the hemolytic anemias which deserves comment. This is the presence of a strong familial and hereditary tendency governing the incidence of certain of the diseases in this group. Hemolytic ictero-anemia and sickle cell anemia are the familiar exemplars of this fact but the erythroblastic anemias of infancy and Cooley's anemia of infants of Mediterranean stock also show a familial tendency which, however, may be due more to conditions of life than to any true hereditary fault. At any rate, the presence of a congenital hereditary fault is not recognized in these syndromes as it is in ictero-anemia and sickle cell anemia. Heredity is an important influence in many diseases of the hemato-lyto-poietic system and is not limited to these hemolytic anemias. For this reason, this aspect of the hemolytic anemias should not be too much emphasized. It is, however, worth noting in passing that blood groupings and allergic sensitivities which may play a part in certain hemolytic processes are also determined by heredity.

Certain of the Hemolytic Anemias Let us now briefly consider certain of the individual hemolytic anemias. (a) Hemolytic ictero-anemia which was formerly called "hemolytic icterus" or "acholic jaundice" deserves special mention for it is so characteristic of the whole group. In this disease, the increased blood destruction seems to depend upon an hereditary congenital abnormality of the erythrocytes which we recognize by the lessened resistance of these cells to hypotonic salt solution in vitro and by their spherical shape. Apparently this defect renders these cells liable to premature hemolysis by the normal erythrocyte destroying mechanisms of the body, and excessive blood destruction is readily induced if anything occurs to increase the conditions favorable to hemolysis. Depending, therefore, on these factors the members of a family with red cells of this type may vary much in their manifestations of disease. One individual will be in apparent health with no anemia and only a slight yellowness of the skin, a slight urobilinuria and a slight enlargement of the spleen. Another will be moderately anemic while a third may be in extreme anemia with fever, a huge spleen, distinct jaundice of skin and blood serum and with much bile pigment and urobilin in the urine. This variability in the activity of blood destruction explains the faulty view formerly held, that there was an acquired form of this disease—the true explanation being that such individuals al-

though born with the same susceptible cells never exhibited the clinical phenomena of increased red cell destruction perhaps until middle age. Often careful questioning will, however, elicit a history of an attack or attacks of previous yellowness which were mistakenly diagnosed catarrhal jaundice, or the family history will contain the record of the death of a child with the picture of an acute infection and severe anemia.

Apparently the margin of safety against hemolysis of the erythrocyte in such individuals must be very narrow for as we have said any intercurrent infection may throw such an individual into a violent erythroclastic crisis which the French term a "crisis of deglobulization." Characteristically the patient has many such episodes of greatly increased blood destruction before coming to the curative operation of splenectomy. Death, if it occurs, does so as a rule from intense anemia after blood regeneration has failed to keep pace with the excessive blood destruction.

The blood picture reveals evidence of the rapid red cell production by the presence of increased numbers of young reticulated erythrocytes—sometimes three-quarters of all the red cells are still youthful enough to exhibit polychromatophilia in the usual stained spread and reticulocytosis when stained with brilliant cresyl blue or some other of the vital stains. Nucleated red cells may be present with the reticulocytosis but not as a rule in the enormous numbers which may appear in certain other hemolytic anemias. Usually many of the red cells in the stained spread appear small and deeply stained. Less high reticulocyte percentages will, of course, be found if hemolysis lessens and eventually in severe cases when the long overworked bone marrow fails, the blood picture may be that of aplastic anemia.

Splenectomy greatly reduces the total of the reticuloendothelial blood destroying tissue and so lessens the degree of hemolysis, it has little or no effect upon the inherent red cell abnormality which being inherited persists through life. It is amazing how much improvement may follow splenectomy in the face of the continuance of the fundamental fault in the erythrocyte.

(b) Sick cell anemia resembles hemolytic ictero-anemia in many ways. Both are characterized by a congenital hereditary familial defect in erythropoiesis. Both are characterized by crises of hemolysis with the same symptoms, the same evidences of increased blood destruction, the same evidences of blood regeneration. Individuals with either of these congenital red cell abnormalities may exist for years without any crisis of hemolysis and without anemia—or may succumb to intense hemolytic anemia. Both may show some degree of bone absorption but this phenomenon is far more marked in certain other hemolytic anemias and will be discussed later.

Differences between the two diseases do, however, exist. The sick cell fault is found almost, if not exclusively, in those of the negro race, the spleen of sick cell anemia while enlarged at first, tends to become fibrosed, contracted and is often markedly adherent to the neighboring peritoneum. Also in the sick cell crisis of hemolysis there is more apt to be abdominal

pain, leg ulcers are more common and gall stones less common than in hemolytic ictero-anemia

Of course, the red cell fault differs in the two, the erythrocytes of sickle anemia are not less resistant than normal to hypotonic salt solution, but do exhibit the typical sickle shape—sometimes in the stained spread and always upon standing in the hanging drop or under any conditions which lower oxygen tension. Even less than in hemolytic ictero-anemia can one see the connection between the abnormality of the red cells and their excessive destruction

(c) So-called paroxysmal hemoglobinuria has been discussed and is only mentioned again because of the many similarities which the individual crises of hemolysis of this syndrome bear to those of hemolytic anemia and sickle cell anemia. It is unfortunate that the name "paroxysmal hemoglobinuria" has been attached to this syndrome for the hemoglobinuria is only an outward and visible sign of a severe hemolytic episode. As we have said, this condition occurs almost exclusively in late syphilis, there is a specific hemolysin present in the blood and the crises of hemolysis are precipitated by exposure to cold. It must be remembered that hemoglobinuria may occur in any hemolytic episode if the amount of liberated hemoglobin is sufficient. Paroxysmal hemoglobinuria is a special case

(d) Next we must mention the so-called idiopathic hemolytic anemias, both acute and chronic. Obviously from their name little or nothing is known concerning their etiology, nor is there any obvious congenital fault in the erythrocytes nor any recognized hemolysin or chemical change in the plasma. Thus even in a field where we know little, these syndromes deserve the term "idiopathic" which is an admission of even greater ignorance. Various eponyms are also applied to these anemias of which Lederer's name is the most commonly used

Again there is a great deal of similarity between the attack of such acute idiopathic hemolytic anemia and the individual episode of hemolysis in one of the other hemolytic anemias we have discussed. Perhaps such an anemia sometimes is the actual unrecognized cause of the so-called idiopathic anemia, in other instances there may be an unidentified acute infection producing an active hemolytic toxin, in still others some allergic incident similar to that in favism may be responsible. Certainly, we must remember not to stress too much the fever and the leukocytosis as evidences of the presence of infection for these symptoms are usually present in hemolytic episodes of non-infectious nature. For the present, we had better admit our ignorance and continue to call these cases "idiopathic" unless we accept as applicable to the whole group what Ham⁴ found in a few cases. As I told you, he demonstrated in cases of chronic hemolytic anemia that the red cells were neither unduly fragile in hypotonic salt solution nor of the sickle cell variety, but were abnormally susceptible to hemolysis in plasma of increased acidity within the normal range as occurs during sleep. If this evidence proves to be widely applicable, it supplies us with a further red cell fault

which would make these cases more nearly analogous to the better understood hemolytic anemias

(e) The only remaining hemolytic anemia entities which need to be discussed are the erythroblastic anemias of infants and Cooley's anemia of infancy and childhood. There is no agreement as to whether these conditions are truly hemolytic, Magner,⁸ for example, in a very recent textbook of hematology, places them all under dyshemopoietic anemias. However, it seems to me that the resemblances which these conditions bear to the better known hemolytic anemias are too great to be ignored. In both the erythroblastoses of infancy and Cooley's anemia, there is a familial incidence, jaundice, splenomegaly, anemia and a markedly regenerative blood picture with enormous numbers of nucleated red cells and young neutrophils and myelocytes. No fault has, however, been demonstrated in the red blood cells although Caminopetros⁹ claims that an increased resistance to hypertonic salt solution is just as constant in Cooley's anemia as the reverse is in hemolytic ictero-anemia. It is hard for me to believe that these anemias are not primarily hemolytic although those who take the opposite view stress the occasional absence of jaundice and the frequent failure to find urobilinogen in the urine. These objections do not seem very important to me, especially when we remember that it is necessary for bile to enter the bowel, there be converted into urobilinogen and then be reabsorbed into the blood, in order for urobilinogen to appear in the urine. In these infants, it may well be that this cycle is not completed.

(f) Miscellaneous. Time will not permit a discussion of the many other episodes of hemolysis from miscellaneous causes, which result in more or less anemia—but it should be said that in general they all resemble the acute crisis of hemolysis in hemolytic ictero-anemia or sickle cell anemia. The acute hemolysis after transfusion of incompatible blood is one example of this, the erythroblastic blood picture of chronic acetanilid intoxication resembles that of certain other hemolytic anemias, the acute hemolytic anemia produced by sulphanilamide resembles a blood crisis in ictero-anemia. It is helpful to keep these resemblances in mind.

THE BONE MARROW AND BONE CHANGES IN HEMOLYTIC ANEMIA

I have carefully avoided trying to describe the bone marrow in the various conditions we have been discussing. I have done this because it is my opinion that there is little to be gained from doing so. During active blood regeneration in response to blood destruction the marrow is red and hyperplastic but we cannot yet surely distinguish the erythropoietic process which floods the circulating blood with reticulocytes from that which frees enormous numbers of nucleated red cells into blood stream. In infancy, we are not surprised to find hemopoiesis still going on in the liver and spleen as well as in the marrow. But when we have made these statements we have said

about all we can and we are not any nearer an understanding of the matter. For the present, it seems better to speak in terms of physiologic processes.

In speaking of the bone marrow it is interesting to remember that osteoporotic changes in the bones themselves occur in a number of the hemolytic anemias. These have been described in hemolytic ictero-anemia, sickle cell anemia and especially in Cooley's anemia. It seems probable that this osteoporosis which appears chiefly in the bones of the skull and the long bones is an evidence of the invasive action of the very markedly hyperplastic red marrow in such cases. In patients with less hemolysis and therefore less active red blood cell production, or in those in whom the process had not continued sufficiently long, the bone changes may be absent. Such bone changes may, therefore, be non-specific and merely the result of very active hemopoiesis and are to be included among the features common to the severe, continuing cases of hemolytic anemia of any kind. This should be subject to experimental proof.

Prognosis and Treatment We come next to the question of the principles of prognosis and treatment of the group of hemolytic anemias. It is easy to say of prognosis, as mathematicians say of so many things, that it is a function of a number of variables. This, of course, is the gist of the matter for the variables are many and include the continuance or cessation of the hemolytic activity, the severity of anemia and the regenerative ability of the bone marrow. If the factor causing the excessive hemolysis can be eliminated, the prognosis will depend upon the degree of anemia already established and the possibility of carrying on with transfusions until red cell production has caught up with the needs of the body. If, on the other hand, one cannot remove or reduce the hemolysis then obviously the prognosis is bad and often eventually hopeless. Individuals with sickle cell anemia have a poor prognosis and the majority die before reaching middle age. On the other hand, hemolytic ictero-anemia is compatible with long life in those in whom there occurs little hemolysis or in whom hemolysis is reduced by splenectomy. In Cooley's anemia, the outcome is always fatal and the prognosis in the erythroblastic anemias of infancy is almost as grave.

The same principles of treatment apply to many of the hemolytic anemias. If hemolysis is severe and anemia is increasing, it is obvious that repeated transfusions may be indicated whether the hemolysis is an isolated incident as in sulphanilamide intoxication or is one episode of a hemolytic ictero-anemia.

Of course, everything must be done to remove the cause, if possible, but where this resides in a congenital fault of the red cells it is apparently impossible to do so. In hemolytic ictero-anemia, therefore, one must accept the continued presence of susceptible red cells but one is able to cut down the hemolysis by removing, by splenectomy, the chief collection of reticulo-endothelial cells. Very beneficial in hemolytic ictero-anemia, this operation is of no value in sickle cell anemia nor apparently in most cases of chronic hemolytic anemia with nocturnal hemoglobinuria, although in an occa-

sional case, splenectomy does seem to give benefit. This led Ham to speculate as to whether the spleen does not provide a region with sluggish circulation and, therefore, a pH sufficiently lowered to predispose to hemolysis of susceptible cells—another example of conditioned hemolysis. Cooley believes splenectomy may prolong life in the disease to which his name is attached, but others do not agree.

It is interesting that in instances of hemolysis following transfusion of incompatible blood there tends to occur severe kidney disturbance with anuria and often with death. This may be prevented or treated, with success in some cases, by the administration of alkali. No such interruption of renal function occurs with the hemoglobinuria which occasionally appears in the episodes of hemolysis of other hemolytic anemias except occasionally in malarial black water fever.

Again, we find ourselves considering treatment in terms of attempted correction of a disturbed physiologic process. Specific treatment we lack. What we can do depends upon our proper interpretation of the mechanisms bringing about the anemia in each patient.

CONCLUSION

We have arrived at the end of our survey of the hemolytic anemias and as is customary we think back over what has been said in the hope of arriving at some definite and useful conclusions. As I do this, I realize that there is little constructive or helpful in what has been said. It has, I am afraid, been destructive rather than constructive. We have found that our knowledge, understanding and treatment of the hemolytic anemias are in a far less satisfactory state than they are in pernicious anemia and the deficiency anemias. We have seen that there is no universal agreement as to which anemias are hemolytic and we have learned that there are a number of different mechanisms of red cell destruction, all of which we casually group together under the term hemolysis. And we are led to suspect that often two agents are active in producing the red cell destruction—one acting only when the cells have been conditioned by the other. We have reviewed a few of the more distinct entities only to find that we are not sure even in these, of the pathogenesis and that our treatment is satisfactory in but few and not specific in any. It is a discouraging state of affairs.

On the bright side, however, a few claims may be made. We have discovered that the anemias grouped together under the term hemolytic have many features in common in their causation, symptoms, manifestation of blood destruction, in the evidences of hyperactivity or erythrocyte production, in the blood pictures and in the principles governing prognosis and treatment. By an appreciation of these group behaviors and by an interpretation of these diseases in terms of disturbed physiology, it would seem that there is hope for a clearer understanding of the whole problem. By visualizing the blood destroying and blood producing mechanisms and tissues as interrelated parts of one system we are led to anticipate and understand

many of the manifestations of a disorder which may in its name suggest a disturbance of but one-half of the hemolytopoietic balance. Ultimate understanding awaits further knowledge and to this end—research in the laboratory and the hospital, study of experimental anemia in animals, and of the disease in man must be continued.

REFERENCES

- 1 BLST, C H, and TAYLOR, N B The physiological basis of medical practice, 1937, Wm Wood and Company, Baltimore
- 2 RHOADS, C P, and BARKER, W H The hemolytic effect of indol in dogs fed normal diets, *Jr Exper Med*, 1938, **lxvii**, 267
RHOADS, C P, and MILLER, D K Induced susceptibility of the blood to indol, *Jr Exper Med*, 1938, **lxvii**, 273
RHOADS, C P, BARKER, W H, and MILLER, D K The increased susceptibility to hemolysis by indol in dogs fed deficient diets, *Jr Exper Med*, 1938, **lxvii**, 299
- 3 PONDER, ERIC Hemolytic properties of indol, *Proc Soc Exper Biol and Med*, 1938, **xxxviii**, 237
- 4 HAM, T H Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria, *New England Jr Med*, 1937, **ccxvii**, 915
- 5 DACIE, J V, ISRAELS, M C G, and WILKINSON, J F Paroxysmal nocturnal hemoglobinuria of Marchiafava type, *Lancet*, 1938, **i**, 479
ISRAELS, M C G, and WILKINSON, J F Haemolytic (spherocytic) jaundice in the adult, *Quart Jr Med*, 1938, **vii**, 137
- 6 SCOTT, R B, ROBB-SMITH, A H T, and SCOWEN, E F The Marchiafava-Micheli syndrome of nocturnal hemoglobinuria with hemolytic anemia, *Quart Jr Med*, 1938, **vii**, 95
- 7 JOSEPHS, H W Studies in hemolytic anemia, *Bull Johns Hopkins Hosp*, 1938, **lxii**, 25
- 8 MAGNER, WILLIAM A textbook of hematology, 1938, P Blakiston's Son and Company, Inc, Philadelphia
- 9 CAMINOPETROS, J Research on infantile erythroblastic anemia in peoples of the Eastern Mediterranean, *Ann d Med*, 1938, **xlui**, 104

THE CURVES OF THYROXINE DECAY IN MYX- EDEMA AND OF IODINE RESPONSE IN THYROTOXICOSIS: THEIR SIMI- LARITY AND ITS POSSIBLE SIGNIFICANCE

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IN 1924 Segall and Means¹ published a curve which represented the average of the basal metabolic responses of a series of thyrotoxic patients to subtotal thyroidectomy, without the previous administration of iodine. They called this the detoxication curve. About a year later Starr, Segall and Means² published a curve similarly obtained and constructed, representing the basal metabolic response of a similar series of thyrotoxic patients to the oral administration of iodine.†

The impressive feature of these two curves was that, save for a post-operative hump on the thyroidectomy curve, the two were, in shape and rate of descent, close to identical.

This identity, or close similarity, of the basal metabolic response of the thyrotoxic person to removal of most of his thyroid, on the one hand, and to the flooding of his system with iodine, on the other, has ever since greatly interested us. At the present time we believe that we can throw some light on its significance.

It is pertinent to point out first, however, that in 1928 Means, Thompson and Thompson⁴ reported further observations on the response of thyrotoxic patients to iodine and drew therefrom certain conclusions. Among these conclusions were the following: (a) that iodine causes a characteristic diminution in the intensity of the intoxication in toxic goiter, (b) that such a response is obtainable at any stage of the disease, and (c) that iodine does not affect the course of the disease. A diagrammatic schema was provided which indicated these relationships.‡

Studies on the iodine response in toxic goiter have been continued and have shown that as biologic reactions go it is an amazingly constant and predictable affair. We have published from time to time composite curves for groups of cases arranged on the basis of preiodine metabolic rate. In figures 1 and 2 will be found our latest study of this sort. The individual curves were those from unselected cases of toxic goiter making iodine responses, in which a level of metabolism had been satisfactorily observed.

* From the Thyroid Clinic of the Massachusetts General Hospital. Presented in abstract to the Association of American Physicians, Atlantic City, May 1937. Received for publication May 16, 1938.

† For graphs, please see the original papers, or MEANS, J H. The thyroid and its diseases, 1937, Lippincott,³ figure 42.

‡ See original paper or MEANS, J H. The thyroid and its diseases, Lippincott,³ 1937, figures 47, 48 and 49.

before iodine administration was begun. Figure 1 shows the actual composite for each group (separation into groups being on the basis of each ten-point interval of preiodine basal metabolic rate) together with the number of cases from which the group average curve was made. The average curve weighted, for the entire lot is shown by the heavy line.

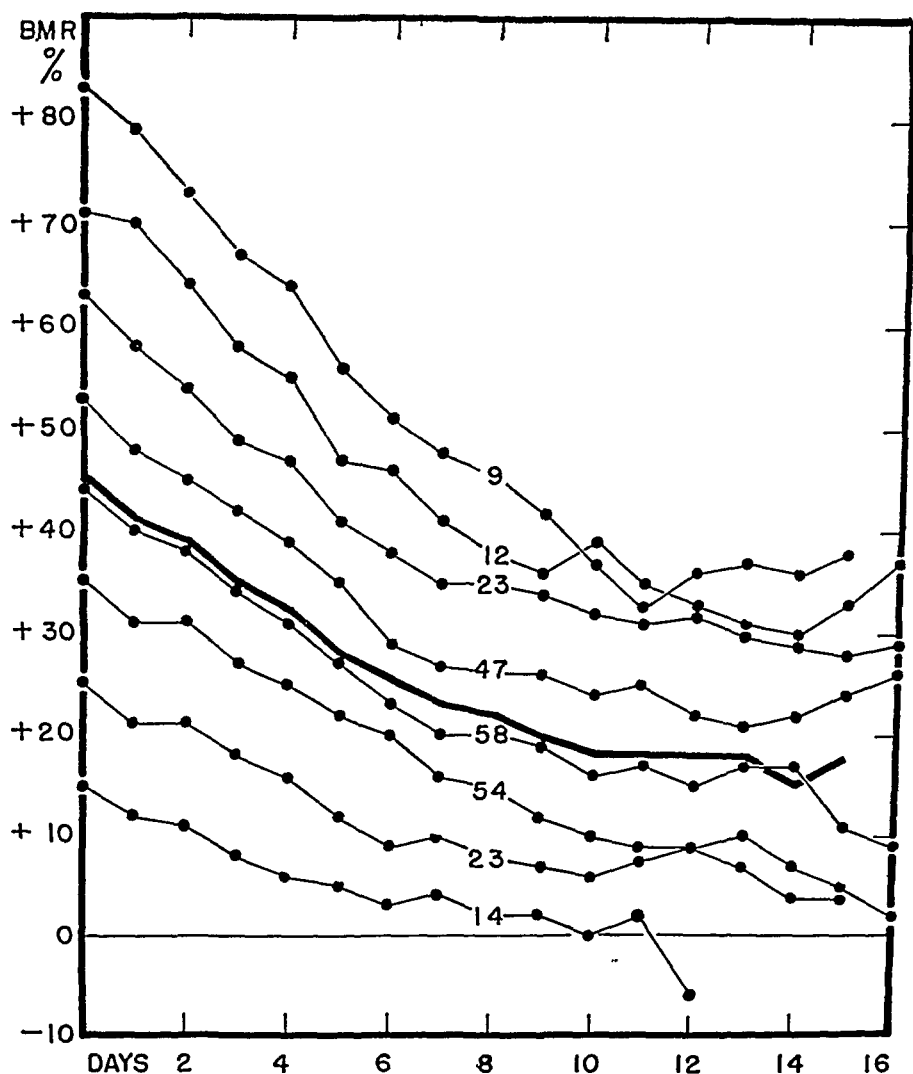


FIG 1 Iodine response in 240 cases of toxic goiter. Divided into groups in accordance with preiodine basal metabolic rate level (Years 1930-35, inclusive). The lines are the composite for each group. The heavy line is the weighted average for the entire group. The numbers on the curves indicate the number of individual cases in each group.

The curves of figure 1, including the weighted average, or composite, were replotted on semilogarithmic paper. On this, up to the tenth to twelfth day they approached straight descending lines, after that, they tended to level off. Absolutely straight lines were then drawn, as closely as possible, through the points up to the twelfth day, and these in turn were replotted on ordinary coordinate paper. The result was the family of

smooth curves shown in figure 2. This graph may be taken to represent what may be reasonably called the standard iodine response.

Another basal metabolic phenomenon of precise and predictable nature is delineated by what Boothby^{5, 6, 7, 8} and his co-workers have called the curve of thyroxine decay. This may be defined as the curve traced by the basal metabolism of a subject whose supply of thyroid hormone is suddenly interrupted. Such a cessation of hormone supply might occur when, in an athyreotic person maintained at a standard level of metabolism by thyroid,

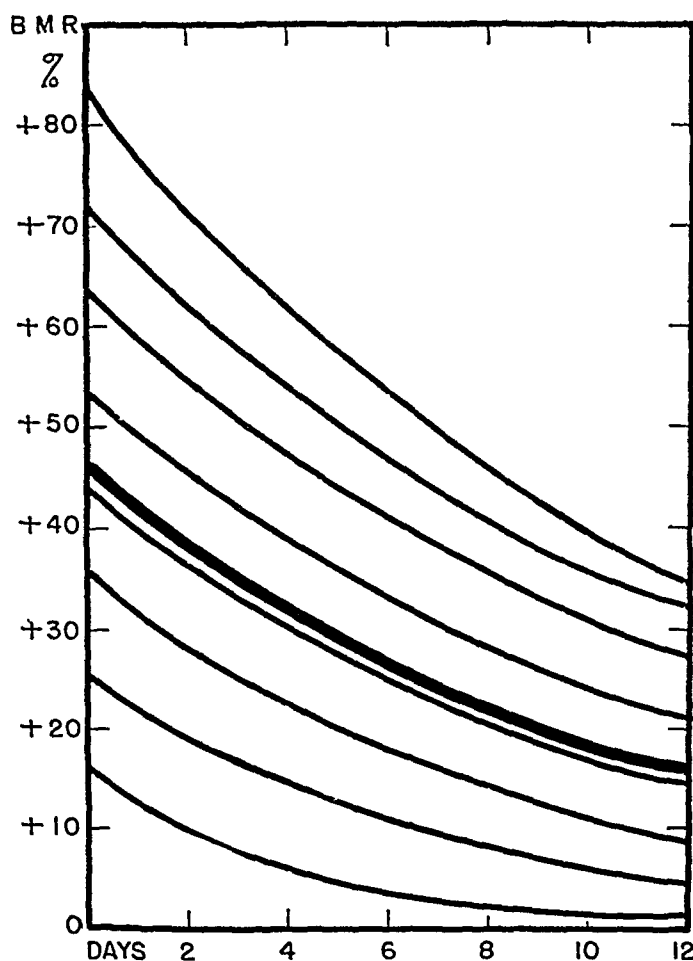


FIG 2 Iodine response in toxic goiter. Same data as shown in figure 1, but smoothed as described in text.

the administration of thyroid was suddenly stopped, or when, in the case of a person possessed of a functioning thyroid, the gland was totally removed. A group of such curves is shown in figure 3. They are very similar in contour one to another. That is to say, stoppage of supply of thyroid hormone produces, as does iodization, in thyrotoxic persons, an amazingly constant result.

It is to be noted that six of the curves in figure 3 are from an approximately standard level of metabolism. A composite has been made of these

six and is shown by a heavy line. Three curves starting above standard are also shown in figure 3 and a composite made of them is also indicated by a heavy line. When the point of origin of the upper composite curve is shifted so that standard metabolism falls on the zero day, then that portion of the composite above standard becomes merely the continuation of the composite of the lower six curves.

As in the case of the iodine response curves, the composite of the six decay curves was plotted on semilogarithmic paper. On this when deducting the limiting value of minus 40, or 60 per cent of standard, from each point, an essentially straight descending line is obtained.

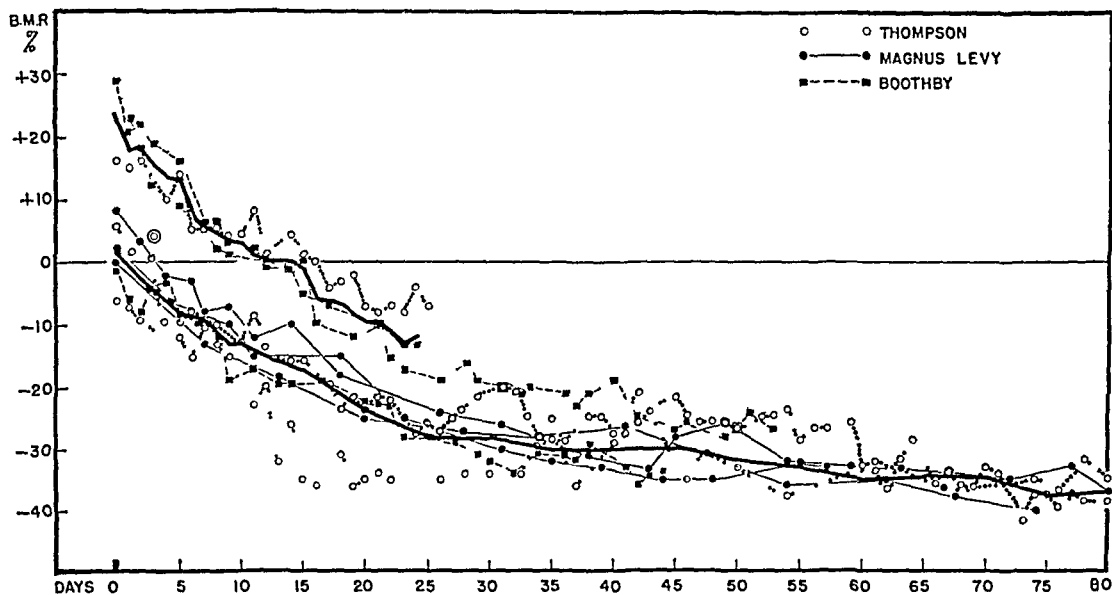


FIG 3 Thyroxine decay in myxedema. Individual curves obtained by various observers, together with two composites, one for six curves starting near basal metabolic rate 0 and one for three curves in the neighborhood of basal metabolic rate plus +20. If the latter is pushed to the left it will be found to form a natural continuation of the former.

The data of thyroxine decay and iodine response suggest curves of the type $y = C + Ae^{-kt}$ or so-called exhaustion curves. Here, y is the per cent of standard metabolism at any given time, t , C the per cent of standard metabolism which the curve approaches as a limiting value, A the increment of metabolism above the limiting value at an arbitrary zero day, and e^{-k} the exponential constant. In the case of thyroxine decay, the limiting value, C , is the myxedema level of minus 40, or 60 per cent of standard, and A becomes 40 if the zero day is arbitrarily chosen at 100 per cent (± 0) of standard. Thus the curve becomes $y = 60 + 40e^{-kt}$. It should be noted that the composite thyroxine decay curve starts at plus 2 in figure 3, but for convenience in calculation the zero day was shifted one day to the right to make it coincide with standard metabolism.

From the composite decay curve of figure 3, the value of k was calculated for each day. These values are more or less uniform up to the 35th day.

This corresponds to that portion of the curve which shows a steady descent and which approximates a straight line on semilogarithmic paper. The remainder of the curve levels off for a few days and then falls at a somewhat slower rate. Consequently the values of k for the first 35 days only were averaged and the average of 0.0421 used in the equation which becomes $y = 60 + 40 e^{-0.0421t}$. The theoretical curve "T" described by this equation is shown in figure 4.

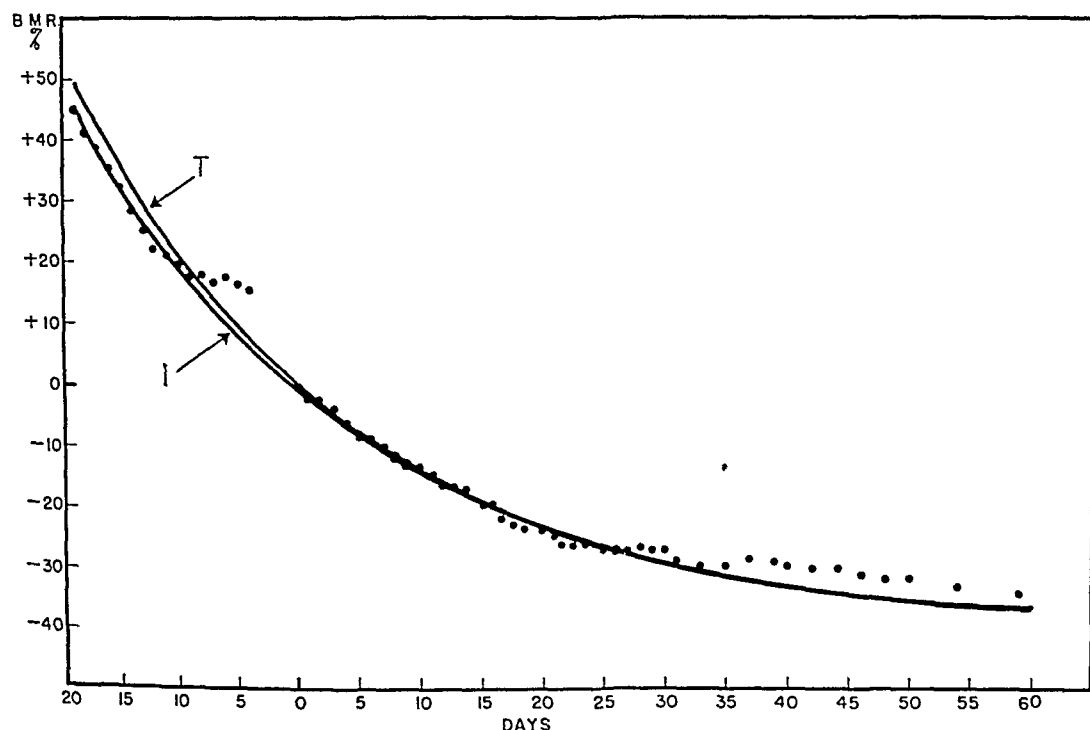


FIG 4 Theoretical curves for thyroxine decay (T) and for iodine response (I), together with the actual points from which they were derived. Curve I was plotted so that basal metabolic rate ± 0 fell on the same day as basal metabolic rate ± 0 for Curve T.

In like manner the composite of iodine response may be represented by a similar equation. However, it is necessary to make one assumption, namely, that the rapidly falling metabolism produced by iodine, if uninterrupted by other factors, would eventually reach the myxedema level of minus 40. That would be true if the delivery of thyroid hormone to the blood were completely blocked by iodine for a considerable period of time. If this assumption holds, then C is 60 in this case also. The metabolism at zero day is 145 per cent and therefore $A = 85$. Thus the equation becomes $y = 60 + 85 e^{-kt}$. The values of k were calculated for the first twelve days and found to vary from 0.0342 to 0.0480, the average being 0.0409. From the equation $y = 60 + 85 e^{-0.0409t}$, the theoretical curve "I" is plotted in figure 4. It is almost identical to curve "T". This we consider a fact of great significance.

These two curves, "T" and "I," may also be constructed mechanically by plotting the data on semilogarithmic paper, after subtracting the limiting

value of 60 from every individual point and then drawing the best possible straight lines through the corresponding groups of points. The curve "I" is prolonged downward and the curve "T" upward. The straight lines and their prolongations are then replotted on ordinary coordinate paper. These are not shown graphically because they are so nearly identical to those shown in figure 4.

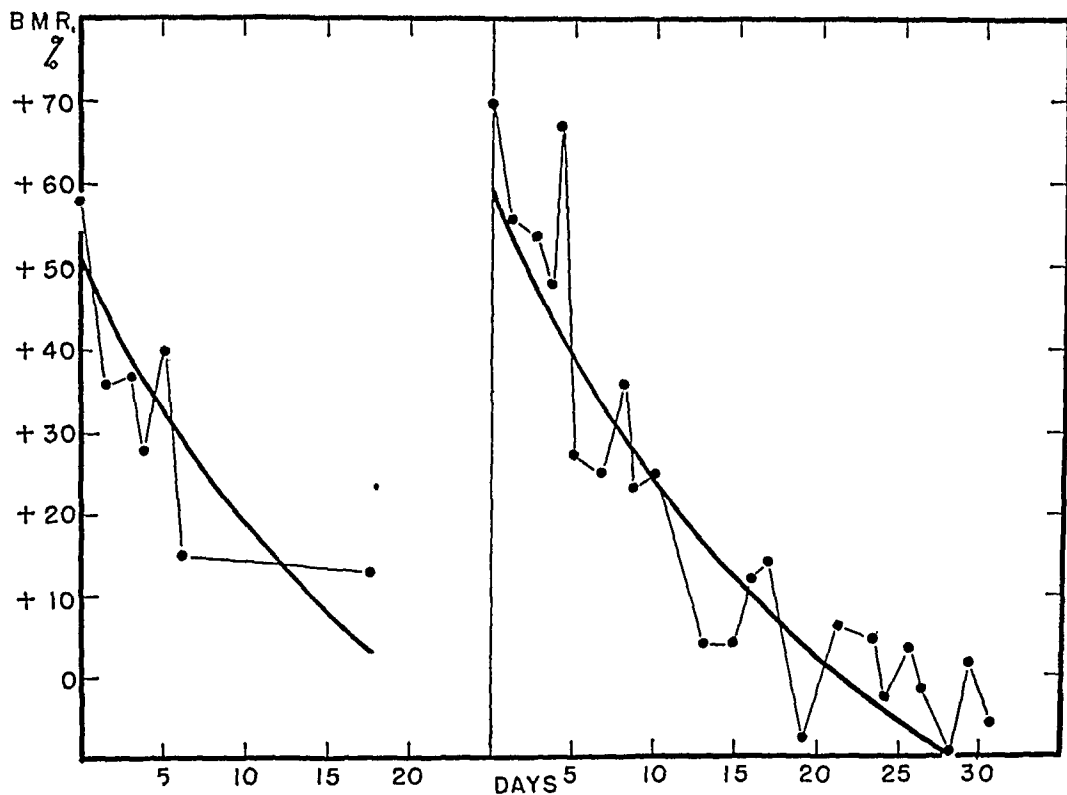


FIG 5 Iodine response and thyroxine decay in same patient. On the left is shown the response to iodine when the patient was naturally thyrotoxic and on the right to cessation of thyroid administration when she was artificially thyrotoxic. To each of these for comparison is fitted Curve T from figure 4.

The curve "T" depicted in figure 4 is essentially similar to the thyroxine decay curves described by Boothby. In fact, it is composed in part of Boothby's data. The exponential equation described by the latter is similar to the one given above. These exhaustion curves, as Boothby contends, may describe a monomolecular type of reaction in which the reacting substance is the concentration of thyroid hormone in the tissues. However, an exponential curve or a straight line on semilogarithmic paper does not necessarily indicate a monomolecular reaction. On this point we concur with Rabinowitch.⁹ We have no means of deciding at present whether we are dealing here with a monomolecular reaction or not. The demonstration by Rabinowitch, that the values of the exponential constant, k , in one curve of Boothby's obtained between daily intervals, vary considerably, is not a valid argument against a monomolecular type of reaction. Experience in-

icates that the decline in metabolism of any one myxedema patient does not follow a smooth curve. As the number of observations increases, the composite approaches a smooth curve. The values of k are bound to vary as much as the individual daily metabolic rates. In our own calculations the values of k up to 35 days were relatively constant.

The actual data from which curves " T " and " I " were constructed are, for comparison, also shown in figure 4. The iodine response data follow curve " I " very closely until the twelfth day is reached, then they flatten out. The thyroxine decay data follow curve " T " very closely, except for an interval between the fortieth and fifty-fifth day. Here the actual data fall above the theoretical curve. This discrepancy may be the result of the small number of observations in this segment of the curve.

A recent case has provided us with some rather unique information which bears upon the relation of iodine response and thyroxine decay.

The patient Miss L. (M. G. H. 340286), aged 26 years, entered the hospital with moderately severe, classic exophthalmic goiter. The curve obtained on iodization is shown in figure 5. She had a subtotal thyroidectomy and postoperatively ran a substandard rate. Psychosis also developed. The Psychiatric Service, to which she was transferred, raised her metabolic rate to about plus 60 by administration of thyroxine (in order to discover whether this would alter her psychosis). On cessation of this medication a decay curve from this high level was obtained. It also is shown in figure 5. The striking feature is that the two curves are essentially alike, although one is due to iodization when the patient was spontaneously thyrotoxic and the other to the stopping of thyroid administration when she was artificially thyrotoxic.

DISCUSSION

Let us now review these facts and consider what they may signify.

First, we have the fact that in spontaneous thyrotoxicosis, taking out most of the thyroid gland has the same, or close to the same, metabolic result as iodization.

Next, we find that the composite curve of thyroxine decay in myxedematous persons and the composite curve of iodine response in thyrotoxic persons appear to be natural segments of a single long curve extending from a high level of basal metabolic rate to a level in the neighborhood of minus 40. At least the upward prolongation of the thyroxine decay curve gives a close approximation to the iodine response curve and the downward prolongation of the iodine response curve gives a close approximation to the thyroxine decay curve.*

Finally, we have an example in one and the same person, Miss L., of the quantitative similarity of the metabolic response to iodine at a time when she was spontaneously thyrotoxic, to that of cessation of thyroid

* Preliminary statements of these relationships have been made in previous publications 10, 11.

medication when she was artificially so. We know that the metabolic curve delineating one of these events was actually one of iodine response, that delineating the other actually one of thyroxine decay, and they are quite alike.

These several facts, all of which indicate the identity, or at least the close similarity, between the effect of iodization of the thyrotoxic patient and thyroidectomy, and between iodine response and thyroxine decay, seem to us consistent with the theory that iodine response in spontaneous thyrotoxicosis actually is dependent on thyroxine decay, that the effect of iodine in spontaneous thyrotoxicosis is to block the delivery of thyroid hormone from gland to body, and serves for a time at least to deprive the subject of hormone as effectively as removal of the hormone factory. This corresponds to the period during which thyroid follicles are filling up with newly-formed thyroid hormone as the result of shift in chemical equilibrium produced by iodine.¹²

Further collateral evidence of thyroid block might be obtained by analysis of blood and other tissues for concentration of thyroid hormone. Thus far direct attempts to measure thyroid hormone have been difficult, although Lunde,¹³ in 1929, reported that the alcohol-insoluble fraction of iodine decreased as the inorganic iodide increased in the blood of patients receiving iodine. Indirect evidence of this decrease in thyroid hormone in the blood has recently been suggested by Salter and Craig.¹⁴ They obtained a "vicarious" or "indirect" elevation of metabolism of surviving tissues treated with blood from hyperthyroid patients. As the basal metabolic rate fell in response to iodine therapy, this "vicarious" metabolic response also declined.

One reservation is in order. Consider for a moment thyroxine decay from a high level. This may be observed either in the thyroidless (e.g. myxedematous) subject or in the normal subject. Should the basal metabolic rate of a totally thyroidless subject be raised to plus 60 by thyroid administration, his metabolism might be expected to fall, upon cessation of thyroid administration, along a curve like curve "T" in figure 4 until a level of about minus 40 basal metabolic rate had been reached. Should the basal metabolic rate of a normal subject be raised to plus 60, however, his basal metabolic rate might be expected to fall, indeed undoubtedly would fall, upon cessation of thyroid administration, along a curve which would start out along the course of curve "T," but which as it approached standard would flatten out, and assume a horizontal course in that neighborhood. This latter is essentially what the curve of iodine response in spontaneous thyrotoxicosis does.

In either of these cases, a course of pure thyroxine decay is approached but not attained. The obvious reason being that a factor other than thyroxine decay enters the picture. That is the power of the subject's thyroid gland to deliver hormone to the body and of this hormone so delivered to raise metabolism. In the thyroidless subject whose thyroid

medication is stopped the metabolism curve is smooth to its base in the substandard zone. It is throughout its entire course a curve of pure hormone decay. In the case of the normal subject, raised to plus 60 basal metabolic rate by thyroid feeding, however, there is a functioning thyroid gland present which will make hormone at a rate which will keep the basal metabolic rate at a near standard level. When thyroid medication is stopped the basal metabolic rate will at first drop along a pure decay curve, but then flatten out as the hormone contributed by the subject's own gland makes its effect apparent. The resulting curve under these circumstances is a pure decay curve in its upper portion only. It is a less simple curve than that displayed by the thyroidless subject. The iodine response curve in spontaneous thyrotoxicosis is of the former sort. It also tends to flatten out somewhere in the neighborhood of standard metabolic rate. It is equal to a pure thyroxine decay curve in its upper portion only. As the thyroid follicle resumes excreting thyroid hormone at a constant rate, a new equilibrium is established.

CONCLUSIONS

The basal metabolic rate curve of thyroid hormone decay has been shown to be closely similar to that of iodination in spontaneous thyrotoxicosis in the following respects:

a Iodination and subtotal thyroidectomy without iodination cause similar metabolic responses.

b The composite iodine response curve of thyrotoxic persons forms a segment of the same curve as that traced by thyroxine decay in myxedematous persons.

c In a single person identical metabolic curves were produced by iodination when the subject was spontaneously thyrotoxic and by withdrawal of thyroid when she was artificially thyrotoxic.

On the basis of these facts the theory is advanced that iodine response in spontaneous thyrotoxicosis is in fact due to thyroxine decay, that the flooding of the system with iodine under such circumstances causes an interruption for a time of the delivery of new hormone from gland to body at large, and that hormone previously delivered decays at the same rate as in the thyroidless subject.

We wish to express our gratitude to Dr. C. R. Doering for help in the mathematical treatment of our data.

BIBLIOGRAPHY

- 1 SEGALL, H. N., and MEANS, J. H. The immediate effect of subtotal thyroidectomy in toxic goiter. Daily basal metabolism and pulse observations, *Arch. Surg.*, 1924, viii, 176.
- 2 STARR, P., SEGALL, H. N., and MEANS, J. H. The effect of iodine in exophthalmic goiter, *Arch. Int. Med.*, 1924, xxiv, 355.
- 3 MEANS, J. H. The thyroid and its diseases, 1937, Lippincott, Philadelphia.

- 4 MEANS, J H, THOMPSON, W O, and THOMPSON, P K On the nature of the iodine reaction in exophthalmic goiter With particular reference to the effect of iodine late in the course of the disease, *Trans Assoc Am Phys*, 1928, *xliii*, 146
- 5 BOOTHBY, W M, and SANDIFORD, I The quantitative estimate of the catalytic power of adrenalin and thyroxin as calorogenic agents and the relative rate of their decay, *Jr Biol Chem*, 1924, *xliix*, 41
- 6 BOOTHBY, W M, SANDIFORD, I, SANDIFORD, K, and SLOSSE, J The effect of thyroxin on the respiratory metabolism and nitrogenous metabolism of normal and myxedematous subjects, *Trans Assoc Am Phys*, 1925, *xl*, 195
- 7 BOOTHBY, W M, and BAIDES, E J Activation and decay curves of thyroxin, *Proc Staff Meet Mayo Clinic*, 1926, *i*, 166
- 8 BOOTHBY, W M, and PLUMMER, W A Diseases of the thyroid gland, Chapter XV-A, 1937, *Oxford Medicine*, Oxford University Press
- 9 RABINOWITCH, I M On the action of thyroxin, *Jr Biol Chem*, 1924-25, *lxii*, 245
- 10 MEANS, J H On the pathogenesis of Graves' disease, *Proc Staff Meet Mayo Clinic*, 1937, *xii*, 11
- 11 MEANS, J H, and LERMAN, J On the similarity of the thyroxine decay curve and iodine response curve in thyrotoxicosis and its possible significance, *Trans Assoc Am Phys*, 1937, *liii*, 26
- 12 SALTER, W T, and LERMAN, J Genesis of thyroid protein, *New England Jr Med*, 1937, *ccxvi*, 371
- 13 LUNDE, G, CROSS, K, and PEDERSEN, O C Untersuchungen uber den Jodstoffwechsel III Untersuchungen uber den Blutjodspiegel bei den primaren Thyreotoxikosen, *Biochem Ztschr*, 1929, *ccvi*, 261
- 14 SALTER, W T, and CRAIG, F N Vicarious metabolic response The oxygen consumption of surviving tissues in plasma from hyperthyroid organisms, *Jr Clin Invest*, 1938, *xvii*, 502

HOW ACCURATE IS THE DIAGNOSIS OF FUNCTIONAL INDIGESTION? A STUDY OF 354 CASES^{*}

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THE diagnosis of functional or nervous indigestion is made so frequently at present that it seems wise to determine, if possible, the accuracy with which the diagnosis is made. Many clinicians find that the majority of patients with dyspepsia who come under their observation fail to present any evidence of significant organic disease, and they are therefore of the opinion in such cases that the indigestion is functional or nervous in origin. In other cases a diagnosis of functional dyspepsia may simply represent the physician's inability for various reasons to discover an underlying organic disease to account for the symptoms.

That dyspepsia of functional or nervous origin is common is indicated by the studies made some years ago by Vanderhoof, Blackford and Dwyer and Foster in which it was found that of 7300 cases of indigestion, in approximately 25 per cent the dyspepsia was of functional origin. In approximately 20 per cent of the cases, systemic disease elsewhere than in the gastrointestinal tract accounted for the symptoms. In approximately 35 per cent of the cases, a reflex cause of the dyspepsia was found in disease of the accessory organs of the digestive tract, whereas in about 14 per cent of the cases there were organic lesions in the stomach and duodenum.

Little evidence has been produced to indicate the accuracy with which the diagnosis of nervous indigestion is made. In an attempt to evaluate this phase of the problem, we have studied the records of 354 patients who after examination at The Mayo Clinic received a diagnosis of functional or nervous indigestion or its equivalent and who were reexamined at the clinic some years later.

In a somewhat similar study of 235 cases in which a diagnosis of chronic nervous exhaustion was made, Macy and Allen found that the diagnosis had been accurate in from 85 to 98 per cent of cases. The actual figure was approximately 94 per cent. In their study chronic nervous exhaustion was used to indicate a "long present, subjective sensation of tiredness, disproportionately exceeding the effort which produces it and which cannot be accounted for by organic disease. Weakness, lack of energy and ambition, nervousness, unrestful sleep, or insomnia, melancholia, tachycardia, and pains and aches in various parts of the body may be additional symptoms of the condition." It is of particular interest in relation to this

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study of dyspepsia of functional origin to note that in Macy and Allen's series the most frequent point of origin of the major symptoms was the gastrointestinal tract (38 per cent of cases) and that the symptoms most frequently noted were bloating and belching, soreness of the abdomen, constipation, eructation, and indefinite types of distress

MATERIAL STUDIED

The records were studied in 354 cases in which the patients returned to the clinic for reexamination an average of 7.33 years (table 1) after the

TABLE I
Interval between Original and Subsequent Examinations in 354 Cases

Interval, years	Cases	Per cent
Less than 5	18*	5.1
5	84	23.7
6	65	18.4
7	66	18.6
8	37	10.5
9	42	11.9
10-15	36	10.2
15-20	4	1.1
More than 20	2	0.6
Average 7.53	354	100.1

* In these cases the original diagnosis of functional dyspepsia was subsequently proved to be questionable or an error

original diagnosis of nervous indigestion, functional dyspepsia, or its equivalent was made at the clinic. By selecting cases in which reexamination was done on one or more occasions after a period of some years, we hoped to be able to trace the cases in which organic disease was a significant etiologic factor and in which it was apparently overlooked at the time of the original examination. It seems reasonable to believe that, if dyspepsia were due to unrecognized organic disease, after a period averaging seven years the development of symptoms and the results of examination would disclose the organic disease in the majority of cases. As Macy and Allen pointed out, the objections to such an assumption seem minor since it is the almost uniform tendency of organic disease to progress and to become more obvious or to improve and to lead to disappearance or diminution of symptoms.

OBSERVATIONS AT PRIMARY EXAMINATION

Character, Incidence and Duration of Symptoms In this group of 354 cases there was a wide diversity of type and duration of symptoms and the clinical pictures resembled those observed in almost all types of gastrointestinal disease. It cannot be concluded readily that any group of symptoms is invariably the result of functional gastric disturbances. Belching, fullness and heaviness in the upper part of the abdomen after eating were

the most common symptoms Nausea, vomiting, eructations of gastric content and relief of symptoms following administration of sodium bicarbonate, other alkalies, or food were next Heartburn was present rather infrequently More than half of the patients stated at the time of the original examination that they were nervous or the presence of this symptom was recorded by the examining physician It has often been stated that symptoms which are functional in origin are characteristically constant in their occurrence However, in a group of 138 cases in this study in which the constant or intermittent character of symptoms was noted, in 76 cases (55 per cent) the symptoms were present intermittently The relation of symptoms to ingestion of food was clear cut in 87 per cent of those cases in which reference to the occurrence of symptoms during the digestive cycle was noted The symptoms occurred before and after meals at widely varying intervals in this group of cases Pain or discomfort in the epigastrium was present in half of the cases in which the situation of pain was noted, in other cases the pain was located in various parts of the abdomen and more rarely in the thorax, back and shoulders The type of painful sensation frequently noted was burning, other patients described their discomfort as gnawing, dull, aching, sharp, cramp-like or colicky or as a soreness, or sense of pressure or heaviness

The duration of symptoms at the time the original examination was made is given in table 2 In 299 cases (85 per cent) the symptoms had been present for at least one year and in many cases the symptoms had extended over a considerably longer period of time

TABLE II

Duration of Symptoms before Original Diagnosis of Functional Dyspepsia in All Cases, with Reference to the Subsequent Diagnosis in Certain Cases

Duration, months	Total cases	Subsequent diagnosis		
		Duodenal ulcer	Gastric ulcer	Gall-bladder disease
Less than 1	6			1
1 to 2	4			
2 to 3	5	2		
3 to 6	16			1
6 to 12	24	2		1
Years				
1 to 2	49	2	1	2
2 to 3	32	3	1	
3 to 4	20	1		
4 to 5	17	1		1
5 to 10	64	4	3	3
10 to 20	53	3		
More than 20	35	1		
Not stated	29			1
	354	19	5	10

Physical and Laboratory Examinations The results of physical examination in almost all instances were essentially negative except that nervousness, abdominal hyperesthesia and tenderness were observed occasionally

Anemia was not a frequent finding In 62.5 per cent of those cases in which the blood was examined the values for hemoglobin were more than 75 per cent (Dare)

Estimations of the levels of free hydrochloric acid in the gastric contents are given in table 3 A wide variation in the values for free hydro-

TABLE III

Values for Free Hydrochloric Acid at the Time of the Original Diagnosis of Functional Dyspepsia with Reference to the Subsequent Diagnosis in Certain Cases

Free Hydrochloric Acid	Patients			Subsequent Diagnosis				
	Males	Females	Total	Duodenal Ulcer	Gastric Ulcer	Gall-bladder Disease		Carcinoma of the Stomach
						Questionable	Stones	
Absent	10	12	22	0	1	0	1	0
0-20*	16	16	32	0	1	2	0	1
20-50*	121	77	198	9	1	1	1	1
50*	64	15	79	8	1	1	3	0
No record	11	12	23	2	1	1	0	0

* Topfer's method

chloric acid was apparent and is about what one would expect to find in a group of normal individuals of the same age and sex

Roentgenologic examinations of the stomach were carried out in most of the cases and in the majority the findings were negative In 23 cases the examination was not done, in three cases the results were indeterminate, and in two other cases a normally functioning gastro-enterostomy was found Examination of the gall-bladder was performed in 90 cases, in 86 the gall-bladder appeared to be normal, in three cases it was reported to be poorly functioning, and in one case the result was indeterminate

RESULTS OF SUBSEQUENT EXAMINATIONS

We have divided our cases into three groups Group 1 consisted of cases in which organic disease was not present at the time of subsequent examination, group 2, of cases in which organic disease of the gastrointestinal tract was found at the time of a subsequent examination, and group 3 of cases in which, at the time of subsequent examination, organic disease was found elsewhere than in the gastrointestinal tract which it was felt may or may not have explained the original symptoms (table 4)

TABLE IV
Summary of Final Diagnosis

Group	Final Diagnosis	Cases	Per cent
1	Functional dyspepsia	303	85.6
2	Organic gastrointestinal diseases	39	11.0
3	Organic disease other than in gastrointestinal tract	12	3.4
Total		354	

Group 1 Organic Disease Not Found at the Time of Subsequent Examination This group is composed of 303 cases (85.6 per cent of the entire group). All of these patients returned to the clinic at least five years (table 1) after the original examination at which time a diagnosis of functional or nervous indigestion had been made. In all of these cases the diagnosis originally made was confirmed at the time of the subsequent examination. Subsequent to the original examination many of these patients had not had symptoms referable to the gastrointestinal tract, other patients had observed an increase or no change in the symptoms, and in the remaining group of cases a diagnosis of functional dyspepsia—its equivalent, or of chronic nervous exhaustion or psychoneurosis was made at the time of the final examination.

This is in reality the least interesting of the three groups. The results suggest a diagnostic accuracy of at least 85.6 per cent for functional dyspepsia in this series. The original diagnosis usually rested on the clinical data which have been mentioned previously and which included evaluation of the gastrointestinal symptoms, the frequent nervous or apprehensive nature of the patient, and the negative results of laboratory and roentgenologic studies.

Group 2 Organic Disease of the Gastrointestinal Tract Found at Subsequent Examination This group consists of 39 patients (11 per cent of the total, table 5). Eighteen of the patients in this group returned to the

TABLE V
Summary of Final Diagnosis in Group 2

Diagnosis	Male	Female	Total
Duodenal ulcer*	18	1	19
Gastric ulcer*	5	0	5
Disease of gall-bladder (proved)*	4	1	5
Disease of gall-bladder (suspected)*	1	4	5
Carcinoma of stomach	2	0	2
Congenital short esophagus	0	1	1
Diverticulosis of colon	0	1	1
Chronic ulcerative colitis	1	0	1
			39

* For time in years between original and subsequent diagnoses, see table 2

clinic within five years of the time of their original examination (table 1) because their symptoms continued and in each instance, a diagnosis of an organic disease was made.

In 19 of the 39 cases a final diagnosis of duodenal ulcer was made and this represented the most common diagnostic error in the series. Other subsequent diagnoses in this group were gastric ulcer, cholecystic disease, carcinoma of the stomach, and so forth. Details concerning the cases in which each diagnosis was made are as follows.

Duodenal ulcer. Eleven of the 19 patients who had a final diagnosis of duodenal ulcer returned to the clinic within a period of five years. Eighteen of the 19 patients were men. Although it is possible that a duodenal ulcer was not present at the time of the original examination, in 14 of these cases the history was characteristic of peptic ulcer. In four cases in which the original story was atypical for duodenal ulcer, a questionable duodenal ulcer was encountered at the time of operation in one case and in two cases, roentgenologic examination was not made at the time of the initial examination. In one case the history only slightly resembled that of duodenal ulcer. In 16 of the 19 cases roentgenologic examination at the time of the first admission gave negative results, subsequently a duodenal ulcer was found. In 17 of these cases in which gastric analysis was made, free hydrochloric acid was present in the gastric content at the time of the original examination (table 3).

This evidence suggests that when a patient gives a characteristic history of duodenal ulcer, when free hydrochloric acid is present in the gastric content and when the duodenum appears normal roentgenologically, care must be exercised in making a diagnosis of functional dyspepsia.

Gastric ulcer. In five cases at the time of the subsequent examination a gastric ulcer was found. It is of interest to note that all of these patients were between 40 and 50 years of age at the time of the original examination, and that all of them at the time of the original examination gave histories similar to those of patients who have ulcer.

Cholecystic disease. Of the 354 cases in only three instances were gallstones found at a subsequent examination. In two other cases operations on the gall-bladder were performed and cholecystitis was found. In none of these cases does review of the original history reveal evidence of colic or jaundice, in fact, the dyspepsia recorded was of an indefinite type.

In five additional cases a final diagnosis was made of probable or questionable disease of the gall-bladder. In three of these cases at the time of the last examination roentgenologic studies of the gall-bladder revealed no abnormalities. The diagnosis of disease of the gall-bladder remains unverified in this group.

Carcinoma of the stomach. In two cases a diagnosis was eventually made of carcinoma of the stomach.

In one case the patient, a man aged 59 years, complained originally of a gnawing pain in the epigastrium two hours after meals over a period of

three to four months. The value for free hydrochloric acid in the gastric content (Topfer's method) was 24 units and for total acid 44 units one hour after the Ewald meal. Roentgenologic study of the stomach gave negative results. Four years later the patient returned to the clinic with the same complaints and on roentgenologic examination was found to have an ulcerating carcinoma at the pyloric end of the stomach.

The second patient, a man aged 34 years, came to the clinic because of a dull epigastric ache which was relieved by the taking of food and which was of five years' duration. The values for free hydrochloric acid in the gastric juice (Topfer's method) was 42 units and for total acid 58 units. Roentgenologic study of the stomach revealed nothing abnormal. A diagnosis was made of functional dyspepsia. Four years later the patient returned to the clinic, at which time he was found to have a carcinoma of the stomach which was resected.

Other types of organic disease of the gastrointestinal tract. In one case each a final diagnosis was made of congenital shortening of the esophagus, diverticulosis of the colon, and chronic ulcerative colitis. There is considerable doubt in the last two cases as to whether the original symptoms were caused by disease in the colon.

Group 3 Organic Disease Found Outside of the Gastrointestinal Tract at the Time of Subsequent Examination. There were 12 patients in this group (table 6). It is extremely difficult accurately to evaluate the re-

TABLE VI
Summary of Final Diagnosis in Group 3

Diagnosis	Cases	Time, Years*
Pernicious anemia	2	1 and 7
Heart disease	2	11 and 9
Syphilis	1	5
Arteriosclerosis	1	4
Hyperthyroidism	1	3
Myxedema	1	5
Kidney stone	1	6
Pulmonary tuberculosis	1	5
Nephritis	1	7
Pituitary tumor	1	6
	12	

* Between original and final diagnosis

lationship of the diseases eventually discovered to the digestive symptoms originally complained of. Gastrointestinal symptoms may occur in all of the diseases noted in this group but review of the histories in these cases shows only two in which a clear-cut relationship could be established between the symptoms originally complained of and the disease eventually discovered. In one case a subtotal thyroidectomy for exophthalmic goiter three years after the original diagnosis of functional dyspepsia led to complete relief of all gastrointestinal symptoms. In another instance review of the history

suggests that the original digestive symptoms could have resulted from a pituitary tumor which was found to be present after a period of six years. In one case the diagnosis of pernicious anemia was made one year following the original diagnosis of functional dyspepsia. At the time of the original diagnosis of dyspepsia this patient who was a woman aged 50 years complained that for three years she had experienced epigastric burning when the stomach was empty. Achlorhydria was present, roentgenologic study of the stomach did not give evidence of abnormality, the value for hemoglobin was 68 per cent (Dare), erythrocytes numbered 3,820,000 per cubic millimeter of blood, and the color index was 0.8. It is quite likely that pernicious anemia was present at the time of the original examination.

COMMENT

If one considers that the cases listed in groups 2 and 3 represent errors in the original diagnosis of functional dyspepsia or its equivalent, the proportion of error is 14.4 per cent, and the accuracy in diagnosis is 85.6 per cent. It is of interest to note that in a group of 354 cases in which a diagnosis of functional dyspepsia was made, examinations after a period averaging seven years revealed evidence of organic gastrointestinal disease in only 11 per cent. Whether it is logical to assume that in all these cases the organic disease was present at the time the original diagnosis was made and was responsible for the symptoms cannot be determined. In some instances, particularly in cases of duodenal or gastric ulcer, this seems likely. If to this group are added the 12 cases (3.4 per cent) in which final examination revealed evidence of a lesion elsewhere than in the gastrointestinal tract the maximal percentage of error is 14.4. It is probable that the actual percentage of error is less than this.

In the study of cases of chronic nervous exhaustion conducted by Macy and Allen, it is of interest to note that the accuracy of diagnosis was found to be between 85 and 98 per cent and actually to be about 94 per cent.

This study leads to the conclusion that when a diagnosis of functional dyspepsia is made after careful examination of the patient and his gastrointestinal tract, the likelihood that the diagnosis is correct is in the neighborhood of at least 85 to 89 per cent. This accuracy of diagnosis compares favorably with that of most other diseases. Analysis of this series of cases suggests that the lesions most likely to be overlooked or to be found or perhaps to develop over a period averaging seven years are duodenal and gastric ulcer and cholecystic disease. Concerning the possible sources of error it seems wise before making a diagnosis of functional indigestion to give much consideration to a patient who is a man and who presents a story suggestive of ulcer. In such cases a diagnosis of functional dyspepsia should be made only after a very thorough investigation, and then it is well to add the reservation that an unrecognized ulcer may be present or may develop subsequently.

It is hoped that as time goes on greater accuracy will be developed in the recognition of organic and functional disease of the gastrointestinal tract. This will be accomplished principally by careful study of patients, recognition of the fact that duodenal and gastric ulcer and disease of the gall-bladder may be overlooked more frequently than other gastrointestinal lesions, and that occasionally unrecognized systemic disease may account for vague or indefinite gastrointestinal symptoms.

In the last few years use of the gastroscope has added another diagnostic procedure which should prove of considerable value in elucidating the diagnostic problem of chronic indigestion. It has been stated that in clinics in which routine gastroscopic studies have been made by experienced observers there is an incidence of some type of chronic gastritis in 28 to 37 per cent of cases of chronic dyspepsia.

SUMMARY

In an attempt to determine the accuracy with which the diagnosis of functional or nervous indigestion is made, we have studied the records of 354 patients who after examination at The Mayo Clinic received a diagnosis of functional or nervous indigestion or its equivalent and who returned and were reexamined at the clinic an average of seven years later. The original diagnosis was confirmed in 303 cases (85.6 per cent). The most common sources of error were duodenal and gastric ulcer and disease of the gall-bladder. It seems reasonable to believe therefore that the diagnosis of functional indigestion can be made with considerable accuracy following a careful examination.

REFERENCES

- 1 BLACKFORD, J. M., and DWYER, M. F. Gastric symptoms with particular reference to gall-bladder disease, *Jr Am Med Assoc*, 1924, lxxxiii, 412-416.
- 2 FOSTER, N. B. The examination of patients, 1923, W. B. Saunders Company, Philadelphia, pp 117-143.
- 3 MACY, J. W., and ALLEN, E. V. A justification of the diagnosis of chronic nervous exhaustion, *ANN INT MED*, 1934, vii, 861-867.
- 4 VANDERHOOF, D. The causes of indigestion. A study of 1000 cases, *Bull Johns Hopkins Hosp*, 1915, xxvi, 151-153.

CLINICAL EXPERIENCES WITH LONG-ACTING INSULIN IN AMBULATORY DIABETIC PATIENTS¹

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SINCE the publication of Hagedorn's article¹ on protamine insulinate in January 1936, followed by the substitution of protamine zinc insulin for protamine insulinate as the result of the work of Scott and Fisher² and the introduction of a new crystalline insulin by Sahyun of Detroit, medical periodicals have been flooded with reports concerning the treatment of diabetes mellitus with these new long-acting insulins.

To review this literature would be superfluous indeed, since it has been adequately summarized in numerous previous articles. The reader interested in a comprehensive survey of the literature on this subject is referred to the papers of Joslin,³ Wilder⁴ and Ricketts.⁵

The advantages of the newer insulins with a prolonged hypoglycemic effect have been thoroughly established. They include a more constant, hence better physiologic, control of diabetes, a reduction in the number of daily injections of insulin and frequently a considerable reduction in the total daily insulin requirement. The various disadvantages accompanying the use of these new insulins have been discussed in detail in previous reports and will not be considered here. Suffice it to say that the magnitude of these disadvantages has steadily decreased with increasing knowledge and experience in the use of these preparations.

The majority of articles have been concerned with the efficacy of protamine zinc insulin after it had been shown to have a more prolonged effect than protamine insulin. Much less has been written concerning the use of crystalline insulin; this has been summarized in a recent report by Altshuler.⁶ The consensus has been that the prolonged hypoglycemic action of crystalline insulin was attributable to its zinc content and that its sphere of prolonged action lay somewhere between that of protamine zinc insulin and regular insulin. Altshuler and Leiser⁷ have shown recently, however, that the prolonged action of crystalline insulin cannot be attributed entirely to its zinc content.

Because our results with protamine zinc insulin agree in general with those reported from other clinics it is not our purpose to encumber the numerous list of articles with additional supporting evidence. The advent of crystalline insulin, however, has provided an opportunity to compare its efficacy with that of protamine zinc insulin in a group of ambulatory patients.

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with uncomplicated diabetes in the Out-Patient Department of the University of California Medical Center. Because our clinical experiences with crystalline insulin have been more favorable than one might expect from some of the previous reports, it is felt their presentation in this paper is warranted.

During the past 18 months we have studied the effect of protamine zinc insulin and crystalline insulin¹ in a group of 52 ambulatory patients chosen at random in the Diabetic Clinic of the University of California Out-Patient Department. There were 37 females and 15 males, the average age of the whole group was 41 years with extremes of 13 to 69 years. The average known duration of diabetes was six years, the extremes being 1 to 17 years.

The patients were grouped arbitrarily according to the severity of their diabetes as follows. Mild diabetics were those controlled on 25 units or less of regular insulin daily, those requiring from 25 to 50 units daily were classified as moderately severe, and those receiving 50 units or more daily were considered as severe.

The degree of control of diabetes in this study was determined by frequent analyses of the urine fractions brought to the Clinic by the patient. The fractional method of urine examination is well known and is employed in many diabetic clinics. Briefly, the method constitutes the collection of four specimens of urine by the patient over a period of 24 hours prior to the visit to the clinic in the following manner:

The patient is directed to collect all the urine voided from breakfast to lunch in one container on the day preceding the visit to the diabetic clinic. A small sample of urine from this bottle is labeled specimen 1 and brought to the Clinic together with samples of urine similarly collected from lunch to supper (specimen 2), supper to bedtime (specimen 3) and from bedtime to breakfast (specimen 4) on the morning of the visit to the clinic. The samples are then tested for glucose by the Benedict qualitative method.

A classification of the degree of control of diabetes was chosen arbitrarily using the following criteria:

- 1 Patients whose urines were consistently negative (no reduction) using Benedict's qualitative test for the presence of glucose, or which showed only occasionally a "green" reduction were considered as well controlled.

- 2 Patients whose urines showed an average "green" to "yellow" reduction were considered as moderately well-controlled.

- 3 Patients whose urines consistently showed an average "yellow" to "orange" reduction were considered as uncontrolled.

This routine was employed both before and after the substitution of protamine zinc insulin or crystalline insulin for regular insulin. Examinations of the urines were made twice weekly following the administration of

* The protamine zinc insulin used in this study was supplied by Eli Lilly & Co. and E. R. Squibb & Sons. Crystalline insulin was supplied by the Frederick Stearns Co.

long-acting insulins until the patients were satisfactorily controlled, then once a week. The average duration of observation of the patients in this group on regular insulin was 29.8 months, the average duration of observation for the same group following the administration of protamine zinc insulin and of crystalline insulin was 7.3 months.

The purely clinical nature of this study and the ambulatory status of the patients, most of whom were employed, and many on relief made frequent blood-sugar determinations impracticable.

It should be emphasized that the dietary regime remained unchanged following the substitution of protamine zinc insulin or crystalline insulin for regular insulin. In our hands the most satisfactory diet has been one with a moderately high carbohydrate content, 150 to 160 grams daily, the daily protein requirement being fulfilled with one gram of protein per kilo body weight. Fats were allowed in amounts necessary to maintain a constant body weight.

Because the majority of the patients studied were employed, and many were on relief, it soon became apparent that the transition from regular insulin to protamine zinc insulin or crystalline insulin would have to be accomplished with a minimal expense and change in the patient's daily routine. Accordingly, the following procedure using either protamine zinc insulin or crystalline insulin was carried out:

1. In substituting long-acting insulin for regular insulin in the treatment of patients with mild diabetes, requiring two doses of regular insulin daily, we usually employed a total daily dosage of the long-acting insulin which was 5 or 10 units less than the amount of regular insulin previously required, and prescribed a single injection in the morning three-quarters of an hour before breakfast.

2. In patients with a moderately severe diabetes receiving three injections of regular insulin daily, we attempted to reduce the number of injections of long-acting insulin to two. At the same time an attempt was made either to maintain the same total dosage or, if possible, to reduce it by 5 to 10 units. If these patients continued to be aglycosuric for several weeks the total daily dosage (units per day) was reduced to a figure consistent with satisfactory control. Among patients in this group who had been receiving only two injections of regular insulin daily an attempt was made to regulate them with only one injection of long-acting insulin and moreover with a lesser number of units per day.

3. In patients with severe diabetes, who received two or more injections of regular insulin daily, the procedure as described above for patients with a moderate diabetes, was followed. In this group, we found protamine zinc insulin U-80 to have the same effect, unit for unit, as the U-40 preparation. The advantage of U-80 protamine zinc insulin in patients receiving more than 40 units at a single injection is obvious.

4. Early in our studies we were influenced by numerous reports, that

the postprandial hyperglycemia, so likely to occur after breakfast using only one dose of protamine zinc insulin in the morning daily, made it advisable to accompany the morning dose of protamine zinc insulin with a small dose of regular insulin. This procedure was carried out in 13 of the patients included in this study.

TABLE I

Per cent reduction both in dosage (units of insulin per day) and number of daily injections following substitution of long-acting insulins for regular insulin in 52 patients

	Crystalline Insulin	Protamine Zinc Insulin	Protamine Zinc Insulin and Regular Insulin
Reduction Average Total Daily Dosage	35%	13%	15%
Reduction Average Number Daily Injections	46%	44%	16%
Number of Cases	16	23	13

Table 1 shows the results of the previously outlined study in 52 diabetic patients, all of whom had been treated with regular insulin. Sixteen were transferred to crystalline insulin, 23 to protamine zinc insulin and 13 to protamine zinc insulin and regular insulin together. The most outstanding results were obtained with crystalline insulin. The average total daily dosage of crystalline insulin was smaller by 35 per cent than the former regular insulin dosage. Using the protamine zinc insulin alone or in combination with regular insulin, the reduction in dosage was only 13 per cent and 15 per cent respectively. The number of injections, when both protamine zinc insulin and regular insulin were employed, was only reduced by 16 per cent from the number formerly required with regular insulin. This was to be expected since the minimum number of injections using both types of insulin must be two.

Better control of diabetes followed the use of both crystalline and protamine zinc insulin as compared to regular insulin. Table 2 shows, how-

TABLE II

Degree of Control of Diabetes in 52 Patients Before and After the Administration of Long-Acting Insulin

	Regular Insulin	Crystalline Insulin	Regular Insulin	Protamine Zinc Insulin	Regular Insulin	Protamine Zinc Insulin and Regular Insulin
Not Controlled	44%	0	17%	9%	30%	23%
Fair Control	18%	18%	17%	17%	30%	8%
Well Controlled	38%	82%	66%	74%	40%	69%
Number of Cases	16	16	23	23	13	13

ever, that the greatest percentage of controlled cases were those changed from regular to crystalline insulin. Whereas 44 per cent of the patients,

who later received crystalline insulin, were not controlled on regular insulin, none were uncontrolled after its administration, the percentage of well controlled cases was correspondingly increased from 38 per cent to 82 per cent. Less striking results were noted with protamine zinc insulin alone or in combination with regular insulin.

Of the 52 patients studied, 19 had severe diabetes according to the criteria outlined previously, 23 were considered as having moderately severe diabetes and 10 had mild diabetes. In order to determine the efficacy of the long-acting insulins in these three types of cases, our data were analyzed separately for each group. The results of this analysis are compiled in tables 3, 4, 5, 6 and 7.

TABLE III

Reduction in Insulin Dosage and Number of Daily Injections Following Substitution of Long-Acting Insulin for Regular Insulin in 19 Patients with *Severe* Diabetes

	Crystalline Insulin	Protamine Zinc Insulin	Protamine Zinc Insulin and Regular Insulin
Reduction average total daily dosage	48%	22%	4%
Reduction average number daily injections	41%	43%	28%
Number of cases	5	8	6

TABLE IV

Degree of Control of Diabetes in 19 Patients with *Severe* Diabetes before and after the Administration of Long-Acting Insulin

	Regular Insulin	Crystalline Insulin	Regular Insulin	Protamine Zinc Insulin	Regular Insulin	Protamine Zinc Insulin and Regular Insulin
Not controlled	60%	0	25%	25%	50%	33%
Fair control	40%	20%	25%	25%	33%	0
Well controlled	0	80%	50%	50%	17%	67%
Number of cases	5	5	8	8	6	6

TABLE V

Change in Daily Dosage and Number of Daily Injections of Insulin Following Substitution of Long-Acting Insulin for Regular Insulin in 23 Patients with *Moderately Severe* Diabetes

	Crystalline Insulin	Protamine Zinc Insulin	Protamine Zinc Insulin and Regular Insulin
Reduction average daily dosage	23%	4% increase	9%
Reduction average number daily injections	59%	40%	5%
Number of cases	6	10	7

TABLE VI

Degree of Control of Diabetes before and after the Use of Long-Acting Insulin in 23 Patients with *Moderately Severe* Diabetes

	Regular Insulin	Crystalline Insulin	Regular Insulin	Protamine Zinc Insulin	Regular Insulin	Protamine Zinc Insulin and Regular Insulin
Not controlled	17%	0	20%	0	15%	15%
Fair control	17%	17%	20%	20%	28%	15%
Well controlled	66%	83%	60%	80%	57%	70%
Number of cases	6	6	10	10	7	7

TABLE VII

Reduction in Dosage, Number of Daily Injections and Degree of Control in 10 Patients with *Mild* Diabetes before and after the Use of Long-Acting Insulin

	Regular Insulin	Crystalline Insulin	% Reduction	Regular Insulin	Protamine Zinc Insulin	% Reduction
Average daily dose	18	17	6%	19.8	17.0	9%
Average number injections daily	2.2	1.6	27%	2	1	50%
Cases uncontrolled	3	0		0	0	
Fair control	0	1		0	0	
Well controlled	2	4		5	5	
Number of cases	5	5		5	5	

The greatest reduction in total daily dosage of insulin (units per day) occurred in the *severe* and *moderately severe* diabetics following the use of crystalline insulin (tables 3 and 5). The average daily dose of insulin in the mild diabetics (table 7) was reduced very little following the use of protamine zinc insulin or crystalline insulin. In this group there was a slightly greater reduction in insulin dosage with protamine zinc insulin. It is of interest to note that following the use of protamine zinc insulin, in the moderately severe diabetics, there was a 4 per cent increase in dosage over the amount of regular insulin previously administered.

The greatest reduction in the number of injections daily occurred in the moderately severe diabetics following the use of crystalline insulin (table 5). The number of injections per day in this group was found to be reduced over 50 per cent as compared to a 40 per cent reduction following the use of protamine zinc insulin, and a 5 per cent reduction using protamine zinc insulin and regular insulin combined. In the mild diabetics a greater reduction in the number of injections daily followed the use of protamine zinc insulin (table 7) and in the severe diabetics the reduction in injections (table 3) was about the same following the use of crystalline and protamine zinc insulin.

An analysis of tables 4, 6 and 7 shows that those diabetics transferred to crystalline insulin were better controlled than those on protamine zinc insulin alone or in combination with regular insulin. This finding was most apparent in the severe diabetics (table 4). In this group the well-controlled cases were increased 80 per cent following the use of crystalline insulin, improvement in control of the mild and moderately severe diabetics was less striking.

It is quite apparent that the use of crystalline insulin in this study has resulted in a reduction not only in the number of injections of insulin daily and the number of units administered per day in the majority of cases, but has improved remarkably the control of the diabetes in all. Similar results were obtained with protamine zinc insulin alone or in combination with regular insulin but to a less striking degree.

While our results with crystalline insulin were entirely unexpected at the time, others have apparently had similar experiences with this preparation. Allen⁸ has found that in the most severe and labile diabetic patients the original hope that protamine zinc insulin would facilitate control of hyperglycemia has not been fulfilled. He has found that crystalline insulin in such cases proved distinctly helpful, despite the fact that its duration of prolonged action was not equal to that of protamine zinc insulin. Our clinical experiences in this work indicate that better results are to be expected with long-acting insulins in the severe and moderately severe diabetics. Patients whose daily insulin requirements are small may be satisfactorily controlled on regular insulin, although the number of injections per day may often be reduced with long-acting insulin. Diabetic patients who are not faithful to dietary limitations, or who are insulin sensitive or resistant, present as great a problem under the administration of insulins with prolonged action as they do with regular insulin. The variability in response to therapy and in cooperation of the patients in this study undoubtedly have had a bearing on these results, for these reasons further studies are desirable. It would seem reasonable to assume, however, that crystalline insulin has a definite place in the treatment of certain diabetics, where the longer action of protamine zinc insulin and its greater accumulative effect may not be altogether desirable.

SUMMARY AND CONCLUSIONS

A group of 52 patients with uncomplicated diabetes previously treated with regular insulin were transferred to protamine zinc insulin and crystalline insulin therapy. These patients were chosen at random and classified as having severe, moderately severe or mild diabetes.

After satisfactory periods of observation under regular insulin therapy and with the insulins of prolonged hypoglycemic activity, we found that this particular group of patients, analyzed as a whole, showed a definite reduction in the average total daily dosage, after the change over to long-

acting insulins. This reduction was greatest among those patients transferred to crystalline insulin. A definite reduction in the average number of daily injections likewise followed the use of long-acting insulins and this was about the same for those patients who received protamine zinc insulin alone and crystalline insulin. Better control of diabetes followed the use of the long-acting insulins. This was most outstanding among the patients who received crystalline insulin.

An analysis of our results with the different types of insulins in patients with diabetes of varying degrees of severity showed that a greater reduction in the total daily insulin dosage followed the use of crystalline insulin in patients with severe and moderately severe diabetes. Among a smaller group of mild diabetics the reduction in dosage was not great and was about the same for crystalline and protamine zinc insulin.

Among the patients with moderately severe diabetes the greatest reduction in the number of injections per day followed the use of crystalline insulin. The reduction in daily injections in the severe diabetics was approximately the same following the crystalline and protamine zinc insulin, whereas in a small group of mild diabetics this reduction was greater following protamine zinc insulin.

Improvement in the control of diabetes was most outstanding in patients with severe diabetes after they had been changed over to crystalline insulin.

BIBLIOGRAPHY

- 1 HAGEDORN, H. C., JENSEN, B. N., KRARUP, N. B., and WODSTRUP, I. Protamine insulin, *Jr Am Med Assoc*, 1936, cvi, 177-180.
- 2 SCOTT, D. A., and FISHER, A. M. Studies on insulin with protamine, *Jr Pharm and Exper Therap*, 1936, lviii, 78-92.
- 3 JOSLIN, E. P. Protamine insulin, *Jr Am Med Assoc*, 1937, cix, 497-503.
- 4 WILDER, R. M. Clinical investigations of insulins with prolonged activity, *ANN INT MED*, 1937, xi, 13-38.
- 5 RICKETTS, H. T. Problems connected with the use of protamine-zinc-insulin, *ANN INT MED*, 1937, xi, 777-790.
- 6 ALTSHULER, S. S. The clinical use of crystalline insulin, *ANN INT MED*, 1937, xi, 901-906.
- 7 ALTSHULER, S. S., and LEISER, R. The effect of zinc content upon the action of insulin, *Am Jr Med Sci*, 1938, cxcv, 234-239.
- 8 ALLEN, F. M. Protamine insulin and diabetes treatment, *Medical Times*, 1937, lvi, 608-610.

THE PRESSOR RESPONSE OF NORMAL AND HYPERTENSIVE HUMAN SUBJECTS TO TYRAMINE INTRODUCED INTO THE ILEUM

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THE recent experiments of Goldblatt and his collaborators have shown that hypertension follows the production of renal ischemia in the dog. The facts that its development is entirely independent of the renal¹ or sympathetic nerves² and that its maintenance depends on the presence in the body of ischemic renal tissue³ suggest that the hypertension so produced is due to a circulating pressor substance. This view is strengthened by the demonstration that kidneys of animals rendered hypertensive by experimental renal ischemia yield on extraction pressor substances in greater amount than do normal kidneys^{4,5}. These observations have stimulated the search both for factors causing primary renal ischemia in man, and for a pressor agent which might be identified consistently in the hypertensive state. Tyramine (para-hydroxy-phenyl-ethylamine), a known vasoconstrictor substance, has been implicated in both respects.

Evidence exists which suggests that tyramine is a pressor agent resulting from renal ischemia, since it has been found in the blood of experimental animals rendered hypertensive by partial occlusion of the renal arteries⁶, on the other hand, recent experiments⁷ have demonstrated that it may be the cause of renal ischemia, for its parenteral introduction into experimental animals for the period of a year resulted in arteriolar nephrosclerosis similar to that observed in the kidneys of hypertensive subjects.

Tyramine taken by mouth in usual doses is totally inactive, but when it was introduced directly into the ileum by means of intestinal intubation we observed a transient but definite rise in blood pressure. This observation made it seem reasonable to reopen the question of whether certain individuals develop primary renal ischemia and secondary hypertension because they lack the normal protection against prolonged exposure to the vasoconstrictor effects of tyramine absorbed from the lower intestinal tract, where bacteria normally present are capable of forming it from tyrosine⁸. Such a lack of protection in hypertensive subjects should make them unusually susceptible to the effects of tyramine. In searching for such susceptibility we have compared the pressor response of normal and hypertensive subjects to the introduction of tyramine into the ileum. The results

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lead us to the conclusion that no significant difference exists between the two groups

METHODS

The subjects were divided into two groups 13 with normal blood pressure and no significant evidence of cardio-vascular, renal or digestive disease, and 13 with hypertension, 6 of the latter having benign or essential hypertension and 7, malignant hypertension. The subjects, who had fasted

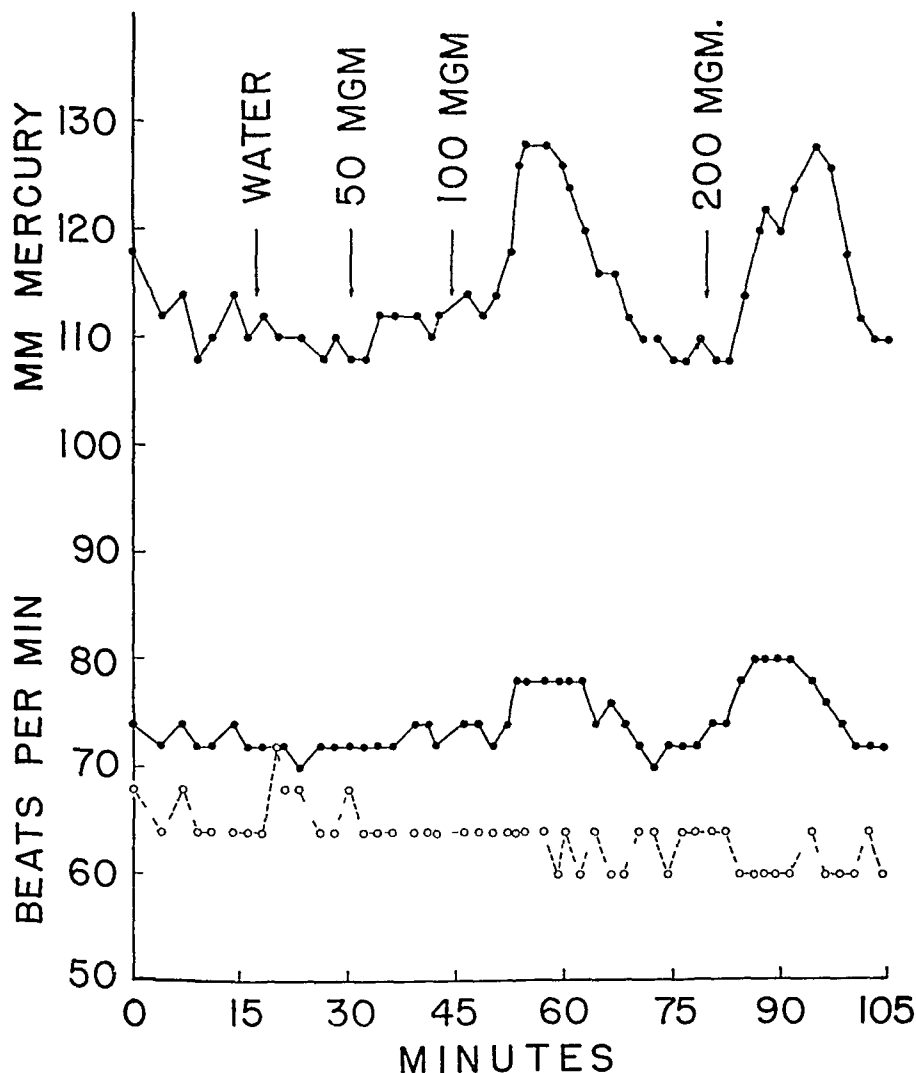


Fig 1 The effect on pulse and blood pressure of ascending doses of tyramine introduced into the ileum of a normal human subject. The open circles indicate pulse rate

for approximately 16 hours, were intubated by the method of Miller and Abbott⁹. A double-lumened tube was introduced, with fluoroscopic guidance, into the duodenum. A small balloon connected with the distal end of one lumen was then inflated with air, and the tube was allowed to progress until its tip was found by fluoroscopic observation to be in the ileum, when further progress was stopped by deflating the balloon. With the sub-

ject lying at rest frequent readings of pulse and of systolic and diastolic blood pressure were made with a clinical mercury manometer. When the readings were reasonably constant 15 cc of water were introduced through the open lumen of the tube, and its effects on pulse and blood pressure were observed. This control measure was necessary since the subjects were all made aware of the introduction of solutions by a sensation of coolness in the throat. Fifty, 100 and 200 mg of tyramine hydrochloride in 15 cc of water were introduced serially, and the responses determined. The exact portion of the ileum into which the tyramine was introduced varied in the different subjects without apparent influence on the results.

RESULTS

The response of a typical normal subject is observed in figure 1. The introduction of water alone produced no detectable effect on the blood pressure and only a slight, temporary increase in the pulse rate. Fifty mg of tyramine were followed by no change whatever, while 100 mg caused the systolic blood pressure to rise approximately 20 mm of Hg and the diastolic only 5 mm of Hg above the resting level. The pulse rate was somewhat slower during the rise in blood pressure. Two hundred mg of tyramine produced an effect essentially similar to that of 100 mg, which is exceptional in that the height of the blood pressure rise was ordinarily proportional to the size of the dose. The blood pressure curve was at its highest point in 12 to 15 minutes and returned to normal in 20 to 25 minutes after the drug was administered. Taking the results as a whole, the blood pressure change was chiefly in the systolic reading, diastolic pressure was either unchanged or very slightly increased. The pulse was usually somewhat slowed or was unchanged. Pallor of the skin was not observed. Subjective symptoms were rare; a few subjects noticed transient palpitation at the height of the blood pressure elevation, but as a rule they had no unusual sensations.

TABLE I

A comparison of reactivity of normal and hypertensive subjects to tyramine. A rise in systolic blood pressure of 10 mm of Hg or more was regarded as a positive response.

	50 Mg		100 Mg		200 Mg	
	Normal	Hyper	Normal	Hyper	Normal	Hyper
Reactive	1	5	5	8	8	2
Non-reactive	12	6	8	3	2	2
Percentage of positive reactors	7%	45%	38%	72%	80%	100%

Table 1 compares the percentage of subjects from both groups regarded as having a significant rise in blood pressure following tyramine. An elevation in the systolic pressure of 10 mm of mercury or more above the rest-

mg level was taken as evidence of drug action since the spontaneous variations during the control period were always distinctly less than this. The average dose per kilogram of body weight was identical in the two groups, 0.8 and 1.6 mg per kilo for the 50 and 100 mg doses respectively. This was also the average dose of the positive reactors in the hypertensive group. It will be observed that the percentage of positive reactors in the latter group was consistently greater, whatever the dose of tyramine. Perhaps a more accurate picture of the observed difference is obtained from comparison in the two groups of the actual curves of systolic blood pressure following the administration of 50 and 100 mg of tyramine (figure 2). Although an

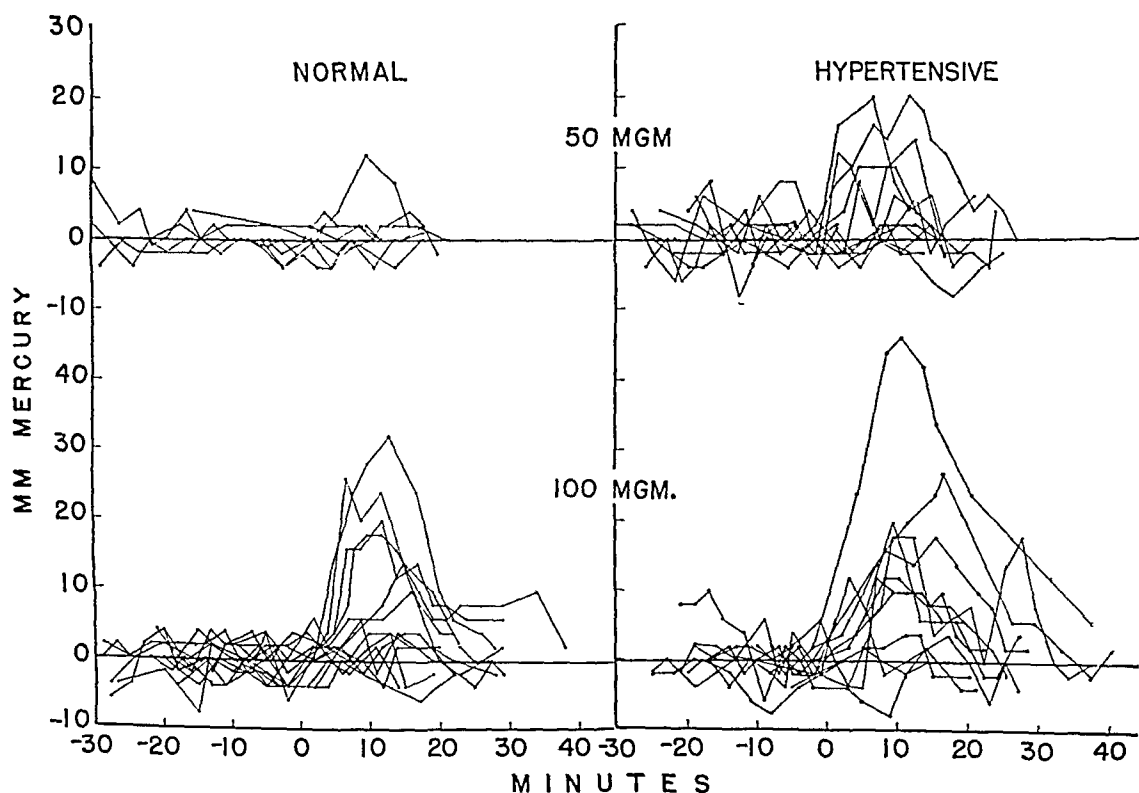


FIG 2 Comparison of the response of normal and hypertensive subjects to the introduction of 50 and 100 mg tyramine into the ileum

obvious difference between the curves is apparent, it will be noted that the time of onset, magnitude and duration of the elevation of blood pressure were much alike. Changes in the diastolic pressure and pulse rate and incidence of subjective symptoms did not differ materially. Thus the character of the response, when it occurred, was more or less fixed, and the chief difference lay in its higher incidence in the hypertensive group.

DISCUSSION

It is conceivable that the inherent defect which ultimately leads to the development of clinical hypertension in susceptible individuals consists in

some abnormality which permits prolonged exposure of the organism to the vasoconstrictor effects of tyramine. Such abnormality might reside either in the intestinal wall, allowing absorption of abnormally large amounts of the substance, in the liver, which normally destroys tyramine reaching it through the portal circulation,¹⁰ or in the peripheral vasomotor apparatus which might be unusually sensitive to its action. If such were the case it seems reasonable to expect that this defect should be disclosed either by an abnormally great or by an excessively prolonged pressor response following introduction of this substance into the lower intestine. Unfortunately absolute criteria of what constitutes a normal response do not exist, hence the interpretation of the results must be a matter of opinion. The present experiments have disclosed that certain of the hypertensive subjects did, indeed, react to tyramine with an elevation of blood pressure distinctly higher, and in some cases, more prolonged than that in the normal subjects. However, for two reasons we do not believe that our data necessarily provide evidence that the concept outlined above is correct. First, it will be observed that some of the hypertensive subjects were totally unreactive to tyramine, others gave normal responses, still others were hyper-reactive. In other words a marked individual variation in susceptibility was demonstrated. This same variability was observed in the normal subjects. If sensitivity to tyramine constituted a fundamental etiologic factor in hypertension it should have manifested itself, in our opinion, with much greater uniformity than was the case. In the second place, it is well recognized that a variety of unrelated stimuli such as cold,¹¹ pain,¹² exercise,¹³ injection of adrenalin¹⁴ and inhalation of CO₂¹⁵ produce abnormally great elevation of blood pressure in hypertensive individuals. The nature of this hyper-reactivity is the subject of discussion,¹⁶ but whatever the cause the variety of stimuli which produce it make one cautious in attributing special significance to tyramine and suggest that the heightened response to this substance in the hypertensive group is an expression of a general, non-specific hyper-reactivity.

Two earlier observations with respect to tyramine in hypertension deserve comment here, since though unrelated to the present experiments they bear on the general problem at hand. Reference has been made to the fact that tyramine administered to experimental animals daily for the period of a year produced nephrosclerosis.⁷ Though extensive vascular and parenchymal changes were present in the kidneys of two dogs so treated, neither developed hypertension. This observation, if substantiated by more extensive data, raises serious question whether the arteriolar nephrosclerosis caused by prolonged tyramine administration is capable of producing permanent hypertension in the same fashion as the more acute reduction of renal blood supply employed experimentally by Goldblatt.

Recent experiments of Landis, Montgomery and Spackman¹⁷ have provided important data relating to the hypertensive action of tyramine, which raise further doubt as to the importance of its rôle in human hypertension.

In studying the effects of a variety of agents on the blood pressure and peripheral blood flow of the unanesthetized rabbit they found certain differences in the circulatory dynamics which appear to be of fundamental importance. All of the pressor drugs studied, including tyramine, produced a rise in blood pressure and with it a definite decrease in the peripheral blood flow. Heated saline extracts of rabbit kidney, on the other hand, produced hypertension without evidence of decreased peripheral blood flow. This is precisely the condition found in human hypertension,¹⁸ and the fact that the hypertension produced by tyramine differs from it in such a fundamental respect further weakens, in our opinion, the belief that tyramine is concerned in the development of human hypertension.

SUMMARY

Tyramine, introduced into the ileum of human subjects by means of small intestinal intubation, produced a transient but unequivocal rise in blood pressure. The response to this substance has been compared in normal and hypertensive subjects. The hypertensive group was slightly more reactive than normal, i.e. the percentage of those having a significant rise in blood pressure was greater, and the pressor response was in general somewhat higher, although its duration was similar. The results are interpreted as further evidence of the lability of blood pressure in hypertensive individuals. The observed difference in response was not considered sufficiently striking to suggest that one of the factors in the etiology of hypertension is a constitutional susceptibility to the effects of tyramine.

BIBLIOGRAPHY

- 1 PAGE, I. H. The relationship of the extrinsic renal nerves to the origin of experimental hypertension, *Am. Jr. Physiol.*, 1935, cxii, 166-171.
- 2 FREEMAN, N. E., and PAGE, I. H. Hypertension produced by constriction of renal artery in sympathectomized dogs, *Am. Heart Jr.*, 1937, xiv, 405-414.
- 3 GOLDBLATT, H. Studies on experimental hypertension, *ANN. INT. MED.*, 1937, xi, 69-103.
- 4 HARRISON, T. R., BLALOCK, A., MASON, M. F., and WILLIAMS, J. R. Relation of kidneys to blood pressure, *Arch. Int. Med.*, 1937, lx, 1058-1068.
- 5 PRINTZMETAL, M., and FRIEDMAN, B. Pressor effects of kidney extracts from patients and dogs with hypertension, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxv, 122-124.
- 6 MÜLLER, P. Technique pour la détermination de la tyramine dans le liquide céphalo-rachidien et le serum sanguin, *Compt. rend. Soc. de biol.*, 1936, cxliii, 128-130.
- 7 PAUNZ, L. Die experimentelle Erzeugung der Nephrosclerose durch Tyramin, *Ztschr. f. d. Gesam. exper. Med.*, 1935, xci, 424-431.
- 8 HANKE, M. T., and KOESSLER, K. K. Studies on proteinogenous amines, *Jr. Biol. Chem.*, 1924, lxx, 835-853.
- 9 MILLER, T. G., and ABBOTT, W. O. Intestinal intubation, a practical technique, *Am. Jr. Med. Sci.*, 1934, clxxvii, 595-599.
- 10 EWINS, A. J., and LAIDLAW, P. P. The fate of parahydroxyphenylethylamine in the organism, *Jr. Physiol.*, 1910-1911, xli, 78-87.
- 11 HINES, E. A. JR., and BROWN, G. E. A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state, *ANN. INT. MED.*, 1933-1934, vii, 209-217.

- 12 PAL, J Gefasskrisen, 1905, S Hirzel, Leipzig
- 13 BARATH, E Arterial hypertension and physical work, Arch Int Med, 1928, xlii, 297-300
- 14 O'HARI, J P Vascular reactions in vascular hypertension, Am Jr Med Sci, 1920, cli, 369-380
- 15 RAAB, W Die Beziehung zwischen CO₂-Spannung und Blutdruck bei Normalen und Hypertonikern, Ztschr f d Gesam exper Med, 1929, lxviii, 337-370
- 16 FATHFREE, T J, and BROWN, G E Digital arterioles of normal and hypertensive individuals, their response to intravenous administration of epinephrine as measured by cutaneous temperature, Am Heart Jr, 1937, xiii, 1-6
- 17 LANDIS, E M, MONTGOMERY, H, and SPARKMAN, D The effects of pressor drugs and of saline kidney extracts on blood pressure and skin temperature, Jr Clin Invest, 1938, xvii, 189-205
- 18 PICKERING, G W The peripheral resistance in persistent arterial hypertension, Clin Sci, 1935-1936, ii, 209-235

CEREBROVASCULAR COMPLICATIONS IN THROMBO-ANGIITIS OBLITERANS

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It is now known that thrombo-angitis is a disease which is not limited to the extremities. In the recent literature much stress has been laid upon the fact that the vascular lesions associated with thrombo-angitis obliterans frequently involve the coronary arteries, or that the disease of the coronary arteries is frequently associated with thrombo-angitis. It is the purpose of this paper to emphasize another complication of thrombo-angitis obliterans, namely, involvement of the cerebral vessels.

We have been able to find in the literature 23 cases in which involvement of the cerebral arteries was associated with thrombo-angitis obliterans of the extremities. These include four cases reported by Averbuck and Silbert¹ (cases 37, 42, 46 and 47), three cases reported by Jager² (cases 2, 3, and 4), two cases reported by Linenthal and Barron³ and two by Foerster and Guttmann⁴ (cases 1 and 2), and one case each reported by Essen,⁵ Lewis,⁶ Gresser,⁷ Spatz,⁸ Livingston,⁹ Merkelbach,¹⁰ Bauer and Recht,¹¹ Stahnke,¹² Kerr and Underwood,¹³ Friedmann,¹⁴ López Albo,¹⁵ and Buerger¹⁶. In addition, Dr. Teresa McGovern of New York City has kindly sent us the records of a patient with thrombo-angitis obliterans who also had marked contraction of the visual fields. While these cases which have been reported may be cases of characteristic thrombo-angitis obliterans, such a diagnosis could not be made certainly from the reports by Essen, Gresser, Jager (case 4), Averbuck and Silbert (case 47), and Lopez Albo because of the presence of diabetes or hypertension, or because the patient was older than most of those with thrombo-angitis obliterans, or because the clinical reports were insufficient.

The diagnosis of thrombo-angitis obliterans involving the peripheral arteries seems reasonably certain from the reports of cases by Linenthal and Barron, Foerster and Guttmann, Merkelbach, Bauer and Recht, Averbuck and Silbert (cases 37 and 42), Friedmann, and Buerger although pathologic studies of the cerebral lesions were not reported. The case of Kerr and Underwood was not reported as being one of thrombo-angitis obliterans with cerebral involvement but as an example of vascular constriction associated with a lesion of the brain. However, we have included it as it may possibly be an example of thrombo-angitis obliterans. In Jager's case 4 there was no report suggesting disease involving the peripheral arteries. However, on pathologic examination the arteries of the lower extremities

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were thrombosed. On microscopic examination of the cerebral and peripheral arteries evidence of degeneration and inflammation was found. In the cases reported by Lewis, Spatz, Jager (cases 2 and 3), Livingston, Stahnke, Averbuck and Silbert (case 41), either the clinical history or the organic changes indicated thrombo-angitis obliterans of the peripheral arteries and pathologic studies of the cerebral vessels were made. In the case reported by Lewis, the nature of the intracranial lesion was not reported. In Stahnke's case there was apparently embolism. In Jager's cases 2 and 3, both inflammation and degeneration were found in the cerebral vessels, and in Averbuck and Silbert's cases 46 and 47, the lesions were apparently entirely sclerotic. Good examples of thrombo-angitis obliterans involving the peripheral and cerebral vessels will be found in Spatz and Livingston's cases.

While the clinical symptoms of cerebral involvement reported by the foregoing authors varied, they did have some common characteristics. Transient neurologic changes, such as hemianopia (reported by Foerster and Guttmann in case 2, Spatz, and Merkelbach), or hemiplegia, which was either transitory or constant or occurred repeatedly (Linenthal and Barron's cases 1 and 2), Lewis, Spatz, Jager (cases 2 and 3), Livingston, Bauer and Recht, Averbuck and Silbert (cases 37, 42 and 46) were noted.

We concluded from a study of the cases reported that patients who have clinical cerebral manifestations of thrombo-angitis obliterans may have cerebral lesions on a different pathologic basis. Since the clinical evidence of cerebral involvement may be the same in these cases, it is impossible to predict the nature of the cerebrovascular lesion when there is clinical evidence of such lesions, as they may be inflammatory, that is, characteristic of thrombo-angitis obliterans, or degenerative, that is, characteristic of arteriosclerosis, or they may represent a combination of these two processes. The finding of sclerotic changes in the cerebral vessels in cases of thrombo-angitis obliterans is in keeping with observations made previously that, in cases of involvement of the coronary arteries in this condition, the pathologic changes are almost uniformly arteriosclerotic in origin (Saphir). The important observation arrived at from study of reports mentioned in the preceding paragraphs is that lesions of the cerebral vessels, while not always characteristic of thrombo-angitis obliterans, may affect individuals with this disease of the extremities who do not have syphilis, hypertension, or diabetes, or other detectable causes for cerebrovascular lesions.

At The Mayo Clinic we have observed 11 patients with thrombo-angitis obliterans involving the extremities who had evidence of vascular lesions involving the brain. Brief reports of these cases follow.

REPORT OF ELEVEN CASES OBSERVED AT THE MAYO CLINIC

Case 1 A man, 50 years old, was admitted to the clinic in September 1932. He had smoked from 20 to 40 cigarettes a day. He had had superficial phlebitis recurrently, and three years previously headaches and vomiting had been followed by

a defect in vision Two years prior to admission he had noticed cramps in his right arm, and coldness and cyanosis of his right hand and fingers These symptoms had become progressively worse A year and a half prior to examination intermittent claudication affected his left leg About six months before this he had fainted but had revived within a few minutes, there was no residual paralysis Six months prior to examination he became faint and there was numbness of the right side of his face and of his hands and he had an impairment of speech These symptoms, however, disappeared quickly At the time of examination pulsations were absent in the left femoral and popliteal arteries and in the posterior tibial and dorsalis pedis arteries bilaterally Neurologic examination gave essentially negative results except for left homonymous hemianopia The blood pressure in the left brachial artery was 110 systolic and 68 diastolic The patient then left the hospital against advice and returned one month later, four days after sudden occlusion of the right femoral artery The findings were essentially as before except that pulsations were absent in the right popliteal artery and there was marked cyanosis of the right first, second and third toes The right leg was amputated in November 1932, and examination of its vessels showed changes characteristic of thrombo-angiitis obliterans Left lumbar sympathectomy was performed in February 1933, at which time thrombosis of the left common iliac and internal iliac arteries and veins was found, there was marked perivascular inflammation In July 1933, the left leg was amputated A letter from the patient's physician stated that he had died of symptoms of myocardial infarction in September 1933

Case 2 A man, 42 years old, was admitted to the clinic in October 1932 He had smoked 10 cigarettes a day since the age of thirteen Eight and three years respectively, prior to examination he had had superficial phlebitis affecting his left calf and for a year prior to examination he had had intermittent claudication affecting his left calf and arch At the time of examination pulsations were absent in the left dorsalis pedis and posterior tibial arteries and were markedly diminished in the right posterior tibial and dorsalis pedis arteries There was an abnormal amount of pallor on elevation of the left foot and abnormal rubor on dependency The blood pressure was 132 systolic and 86 diastolic Bilateral lumbar sympathectomy was performed in October 1932 On the seventh day following operation it was discovered that the patient was unable to move his right arm and leg and that he was unable to talk At the time of examination there was evidence of right hemiplegia He returned to the clinic in April 1933, at which time there was evidence of improvement, the hemiplegia, however, was again present when he was reexamined in August 1936 There was no evidence of progression of the arterial lesions, although the patient subsequently had superficial phlebitis

Case 3 A man, 37 years old, was examined at the clinic in March 1930 He had smoked 20 cigarettes a day for many years For three years he had had claudication involving the left leg He gave a history suggestive of recurrent phlebitis involving the legs and arms for the previous two years For one year there had been ulceration of the toes of the left foot and fatigue in the right hand when writing Six months prior to examination an ulcer had developed on the right index finger, and two weeks prior to admission to the hospital the left second toe had been amputated Examination showed occlusion of the radial, ulnar, posterior tibial, and dorsalis pedis arteries, bilaterally, and of the left popliteal artery, pulsations were diminished in the femoral artery, bilaterally, and in the right popliteal artery There was a gangrenous wound where the left second toe had been amputated previously The blood pressure was 130 systolic and 86 diastolic One year after examination at the clinic, left hemiplegia occurred from which recovery was complete in several weeks This was followed by another episode of hemiplegia from which the patient recovered only very slowly

Case 4 A man, 39 years old, was examined at the clinic in September 1930

He had had intermittent claudication involving the legs for six months. Superficial phlebitis had been absent. On examination pulsations were found to be absent in the posterior tibial and dorsalis pedis arteries, bilaterally. The blood pressure was 94 systolic and 60 diastolic. One year after dismissal from the clinic we were informed by letter that he had had hemiplegia involving the left side.

Case 5 A man, 47 years old, was examined at the clinic in February 1935. Two years previously he had sustained left hemiplegia, from which he gradually recovered. He had passed a life insurance examination at the age of 42, but at the time the hemiplegia occurred the blood pressure was said to have been 210 systolic. One year prior to admission to the clinic he had noted bilateral claudication in his aches and calves, about seven months later trophic changes developed in the toes of the right foot and the toe nails had to be removed. On examination at the clinic pulsations were absent in the posterior tibial, dorsalis pedis, and popliteal arteries bilaterally. Gangrene of the distal part of the right first toe and two areas of superficial phlebitis below the right knee were present. The blood pressure on several occasions was found to range between 140 and 95 systolic and 85 and 60 diastolic. There was a residual facial weakness, awkwardness and slowness of the left hand, increased deep reflexes of the left arm, positive Hoffman's sign on the left, and a questionable positive Babinski on the left. Amputation of the left leg was performed February 21, 1935. Examination of the vessels of the amputated extremity showed changes characteristic of thrombo-angitis obliterans. A short time after leaving the clinic the patient died suddenly with what was said to have been evidence of a cerebrovascular accident.

Case 6 A man, 35 years old, was examined at the clinic in July 1929. He had had symptoms of vascular disease involving his lower extremities for five years and pains in the fingers of his left hand for three years. He had also had three severe attacks of pain in the left pectoral region, without projection but associated with dyspnea, the longest attack having lasted 20 minutes. Following this the pain had recurred on exertion, and especially in cold weather, it was relieved by nitroglycerin and rest. He had had a primary syphilitic infection in 1924. On examination at the clinic there was marked impairment of pulsations in the dorsalis pedis and posterior tibial arteries bilaterally, and in the left dorsalis pedis artery, marked blanching on elevation of the right foot, and less so on the left, and a moderate degree of abnormal rubor when the feet were dependent were noted. Trophic changes involved the nails of both feet. The blood pressure was 155 systolic and 90 diastolic. The flocculation test on the blood was positive but that on the spinal fluid was negative. The spinal fluid contained two cells per cubic millimeter. Diagnoses of thrombo-angitis obliterans, angina pectoris, and latent syphilis were made. Two years after leaving the clinic we were informed that the patient had sustained a cerebrovascular accident with impairment of speech.

Case 7 A man, 39 years old, was examined at the clinic in September 1930. At the age of 36 he had sustained a right hemiplegia from which he recovered in three weeks. He had known of the existence of hypertension for only six months prior to his examination at the clinic. Eighteen months after the hemiplegia, intermittent claudication of the right leg had developed and intermittent claudication had subsequently affected the left leg also. At the time of examination the blood pressure ranged from 140 to 220 systolic and from 80 to 128 diastolic. Examination of the ocular fundi showed arteriosclerosis, grade 1. Pulsations were absent in the popliteal and dorsalis pedis arteries, bilaterally, and in the left femoral and posterior tibial arteries, they were impaired in the right radial artery. There was abnormal pallor with elevation of the left foot. There was no evidence of hemiplegia. A serologic test for syphilis was negative.

Case 8 A man, 43 years old, was examined at the clinic in June 1932. At the age of 29 years he noticed weakness involving his right arm, which in one to

two hours had progressed until right hemiplegia was complete. The right side of his face was paralyzed and aphasia was present. This paresis persisted for two months and then gradually improved. At the age of 42 he noted intermittent claudication involving his left calf and shortly thereafter rest pain in his left foot, which necessitated amputation of the leg. Pulsations were absent in the right popliteal, posterior tibial, and dorsalis pedis arteries and in the left ulnar artery. There was marked abnormal pallor and rubor of the right leg on dependency and elevation. The flocculation test for syphilis on both blood and spinal fluid was negative. Neurologic examination showed evidence of a residue of a right hemiplegia. The blood pressure was 134 systolic and 88 diastolic.

Case 9 A man, 49 years old, was first examined at the clinic in July 1931. He had had intermittent claudication involving the right calf for four months and superficial phlebitis about three months before admission. His blood pressure was 190 systolic and 110 diastolic. At the time of examination pulsations were absent in the right popliteal, posterior tibial, and dorsalis pedis arteries. Examination of the ocular fundi showed mild narrowing of the retinal arteries. A serologic test for syphilis was negative. The patient was re-admitted to the clinic in January 1932, at which time he had symptoms of duodenal ulcer. The condition of the vascular disease was unchanged. The patient was again examined at the clinic in May 1933, because of more difficulty with the ulcer, and at that time posterior gastroenterostomy was performed for chronic duodenal ulcer with obstruction. His blood pressure was 120 systolic and 70 diastolic. The patient again returned to the clinic in September 1933, stating that five weeks previously he had noted numbness and weakness in his left hand and in his face and that ten days before admission he had twitching involving his left hand and leg, this, however, had disappeared in a short time. He was again reexamined at the clinic in June 1934, at which time he stated that six weeks previously, during excitement, he had become dazed and had got into his car and apparently bumped into some other cars while trying to get out of a parking space. He did not remember much about the drive home. After a day or so the confusion cleared somewhat but he still had some difficulty with his speech. His local physician reported that he had been unconscious for about 24 hours. He was in the hospital for a time and, on one occasion, felt twitching in the left side of his face. His wife said that he forgot easily and repeated frequently. Superficial phlebitis had occurred. Neurologic examination at the clinic gave essentially negative results. The blood pressure varied between 145 and 128 systolic and was 70 diastolic. Examination of the ocular fundi showed normal retinal vessels. The popliteal, posterior tibial, and dorsalis pedis arteries were occluded bilaterally. On April 27, 1934, the patient had an attack with slight paralysis of the face and arm which lasted but a few days. He then got along splendidly after this episode except that his mental confusion did not disappear. On May 12 he had another attack, somewhat slighter than the first. The paralysis again cleared up but mentally the patient became more confused than before.

Case 10 A Jew, 59 years old, was examined at the clinic in May 1929. He had had intermittent claudication since the age of 45 and several severe attacks of superficial phlebitis. At the time of examination the dorsalis pedis, posterior tibial, and popliteal arteries were occluded bilaterally, and the pulsations were diminished in both femoral arteries and absent in the left ulnar artery. On numerous examinations the serologic test for syphilis was negative and the blood pressure was always normal. Since the age of 28 he had had episodes of mania, depression, obsessions, and disorders of affection. In 1929 neurologic examination was negative, there was, however, some evidence of an affective disorder at that time. According to a letter from his physician in January 1934, he had had transitory aphasia and disorientation, and in 1935 he had experienced numbness of the left upper and lower extremities. In October 1935, neurologic examination showed diminished sensations

in, and diminished power and atrophy of the muscles of, the lower extremities. This was considered to be due to neuritis. The patient was reexamined at the clinic on several occasions, the last one being in October, 1936, at which time amputation of the right leg was necessary.

Case 11 A man, 52 years old, had had intermittent claudication involving the lower extremities beginning 20 years earlier. Amputation of both legs below the knees had been performed. For five years he had attacks of pain in the abdomen for which three exploratory operations had been performed. No organic disease was found. Since the age of 48 he had noticed color changes of a vasospastic nature in the fingers of both hands, and trophic lesions finally affected his fingers. At the time of examination at the clinic the patient complained chiefly of pain in both hands. Examination revealed absence of pulsations in the radial and ulnar arteries and in the popliteal arteries bilaterally. Pulsations were diminished in the left femoral artery. The blood pressure was 110 systolic, 85 diastolic. There was no evidence of diabetes or syphilis. Ulcerations were present on some of the fingers. Hemianopia was also present. A diagnosis of thrombo-angitis obliterans was made and, after treatment with repeated intravenous injections of typhoid vaccine to induce fever artificially, and after other measures, cervicothoracic sympathectomy was performed. Convalescence was satisfactory until the twenty-second day following operation when the patient noted the sudden onset of numbness on the left side of his body associated with a marked reduction in motor power. These symptoms persisted for three days and disappeared spontaneously. The hemianopia disappeared after operation. The patient left the clinic much improved but, one year later, wrote that he was having episodes of pain suggestive of angina pectoris and further trouble with vascular disease involving his upper extremities.

It is admitted freely that some of our patients were in the age group in which sclerotic changes might be present. The patients in cases 1, 10 and 11 were 50 or more years old, although in the first case the inflammatory nature of the lesions in the extremities was proved microscopically and in the tenth case the disease was first manifest when the patient was 45 and superficial phlebitis had occurred. In all of our cases there was distinct evidence of organic intracranial disease. In case 10 episodes of aphasia, disorientation, and numbness of the left upper and lower extremities were highly suggestive of organic intracranial disease.

The diagnosis of thrombo-angitis seemed warranted in all cases, although the possibility of the diminished circulation to the extremities being due to arteriosclerosis in some instances, cannot be denied. Hypertension was present in cases 5, 7 and 9 and may possibly have been responsible for the cerebral lesions, although we do not believe so. In all other cases hypertension was absent. None of the patients had diabetes. In case 6 there was a history of syphilis, a flocculation test on the blood was positive while that on the spinal fluid was negative. In all other cases flocculation tests on the blood were negative. Since there was no evidence of syphilis of the central nervous system in case 6, we do not believe the cerebral vascular lesions were due to syphilis.

The duration of the peripheral disease in our group of cases varied from five months to 20 years. In most of the cases the cerebral complications occurred following the onset of the peripheral disease. The cerebral lesion

preceded the peripheral symptoms in only three cases (5, 7, 8) In these three cases the hemiplegia was present two, one, and fourteen years, respectively, before the onset of the peripheral symptoms Thrombo-angitis obliterans must therefore be suspected in cases of cerebral vascular disease of obscure etiology

The outstanding symptom from the neurologic standpoint was hemiplegia which occurred transiently, one or several times, or permanently In some cases there were such symptoms as confusion, disorientation, aphasia, and loss of memory, symptoms which frequently cleared up entirely Hemianopia, which was present in cases 1 and 11, disappeared following sympathectomy in one case (case 11) This is similar to the case reported by Foerster and Guttmann

The symptoms of thrombo-angitis in the brain depend chiefly on where the lesion is located in the brain, and this may vary from case to case Certain manifestations of the disease, however, are predominant and fairly characteristic of cerebral involvement In many cases some of the manifestations of cerebral involvement are transient and disappear entirely Psychic changes, such as confusion and loss of memory, may be associated with signs of organic involvement of the brain Hemiplegia may occur repeatedly or persist The transient nature of the symptoms may be due to arterial spasm superimposed on a thrombotic lesion or to rapid development of collateral circulation after thrombosis Very interesting was the prompt effect of operation on hemianopia in Foerster and Guttmann's case and in our case 11

Our 11 patients with cerebral involvement were from a group of 500 with thrombo-angitis obliterans of the extremities While this percentage of cerebral involvement is only about 20, it may be found that this complication occurs more frequently if attention be directed to it This study emphasizes that cerebrovascular complications may occur in cases of thrombo-angitis obliterans and may precede evidence of the thrombo-angitis obliterans of the extremities It is also apparent that peripheral thrombo-angitis obliterans may be the least serious part of a disease which may be disabling or may terminate life as a result of involvement of such vital structures as the brain and heart

SUMMARY

To reports of 23 cases of thrombo-angitis obliterans with involvement of the brain which have been collected from the literature, reports of 11 cases observed at The Mayo Clinic have been added Too little evidence relative to the nature of the pathologic process in the brain is available, but it may be sclerotic alone, both inflammatory and sclerotic, or inflammatory alone Hemiplegia, hemianopia and psychic changes are common manifestations of cerebral involvement in thrombo-angitis obliterans, and the disappearance and recurrence of these symptoms is occasionally striking

It is apparent that thrombo-angitis obliterans may be a widespread disease and that involvement of the peripheral vessels may be, for some individuals, the least important part of a disease which may involve such vital structures as the heart or brain

REFERENCES

- 1 AVERBUCK, S H, and SILBERT, SAMUEL Thrombo-angitis obliterans IX The cause of death, *Arch Int Med*, 1934, liv, 436-465
- 2 JAGLER, ERNST Zur pathologischen Anatomie der Thromboangitis obliterans bei juveniler Extremitatengangan, *Virchow's Arch f path Anat u Physiol*, 1932, cclxxiv, 526-583
- 3 LINENTHAI, HARRY, and BARRON, M E Thrombo-angitis obliterans—a generalized vascular disease, *Med Clin N Am*, 1929, viii, 229-236
- 4 FOERSTER, O, and GUTTMANN, L Cerebrale Komplikationen bei Thromboangitis obliterans, *Arch f Psychiat*, 1933, c, 506-515
- 5 ESSEN, K W Hemiplegie bei Endarteritis obliterans, *Deutsch Ztschr f Nervenhe*, 1935, cxxxiii-cxxxiv, 99-101
- 6 LEWIS, DEAN Spontaneous gangrene of the extremities, *Arch Surg*, 1927, xv, 613-626
- 7 GRESSER, E B Partial occlusion of retinal vessels in a case of thrombo-angitis obliterans, *Am Jr Ophth*, 1932, xv, 235-237
- 8 SPATZ, H Über die Beteiligung des Gehirns bei der v Winiwarter-Buergerschen Krankheit (Thrombo-endangitis obliterans), *Deutsch Ztschr f Nervenhe*, 1935, cxxxvi-cxxxvii, 86-132
- 9 LIVINGSTON, W K Skin temperature studies III Case report—thrombosis of arteries of extremities, brain, heart and kidney, with a general discussion of vascular disease, *West Jr Surg, Obst and Gynec*, 1933, li, 21-25
- 10 MERKELBACH, O Endarteritis obliterans Winiwarter Homonyme Hemianopsie und Spontanangran an der unteren Extremität Beiträge zur Frage der Endarteritis obliterans durch Kalteschädigung und nach Trauma, *Ztschr f klin Med*, 1933, cxxiv, 66-85
- 11 BAUER, JULIUS, and RECHT, GORG Über spastische und obliterierende Gefassprozesse mit und ohne ischämische Ernährungsstörungen, *Wien Arch f inn Med*, 1932-1933, xxiii, 11-36
- 12 STAHNKE, ERNST Zur Frage der Spontanextremitätennekrose und ihrer Erklärung im Sinne v Winiwarter's als primäre Endarteritis obliterans, *Zentralbl f Chir*, 1928, lv, 914-918
- 13 KERR, W J, and UNDERWOOD, F J Hemiconstriction of the vascular system associated with cerebral disease, *Am Heart Jr*, 1936, xii, 713-723
- 14 FRIEDMANN, R Ein Fall von Thrombo-angitis Obliterans Sitzungsberichte des Vereines f Psychiatrie und Neurologie in Wien (11, Nov 1930) in *Jahrbucher für Psychiatrie*, 1930-1932, xlvii-xlviii, 59-60
- 15 LOPEZ, ALBO, W Forma cerebral de la tromboendangitis obliterans de Winiwarter-Buerger con motivo de una observacion clinica, *An de med int*, 1935, iv, 707-719
- 16 BUERGER, LEO Thrombo-angitis obliterans—pathology in lethal cases *In The circulatory disturbances of the extremities*, 1924, W B Saunders Company, Philadelphia, chapter LXIII, p 371 (case 3)

CARDIOVASCULAR CHANGES ASSOCIATED WITH THE INSULIN SHOCK TREATMENT¹

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ALTHOUGH Sakel's insulin "shock" treatment for schizophrenia has been receiving increasing recognition during the past three years, and has already been employed in thousands of cases, there have appeared comparatively few thorough or exhaustive works regarding the physiological changes associated with this method of therapy. This has been especially true as regards the description of changes in the circulatory system. No doubt this has been to a large extent due to the preoccupation of the various workers with the psychic rather than physical changes undergone by the patients, during and after the course of insulin "shock". Also Sakel has specifically admonished his followers against unduly disturbing the patients with unessential tests or examinations during the treatment, inasmuch as this would interfere with their obtaining and maintaining an optimal state of "shock". This prohibition must have led to the failure of many workers to recognize certain definite circulatory changes which a closer degree of observation would undoubtedly have disclosed. Consequently, it is not surprising that the most thorough and reliable studies on circulatory changes under the influence of insulin have been conducted by workers such as Weichmann and Koch,¹ Brandt and Katz,² Romano, Mazzei and Baila,³ who approached the subject from the experimental angle, rather than under the clinical conditions of the Sakel regimen.

It is our purpose in this paper to collect and organize the data available at present regarding the changes in the circulatory system during prolonged insulin hypoglycemic treatment and to amplify and confirm some of these findings with the material obtained from our own observations. Our own observations were based on the detailed study of a group of male patients, all suffering from schizophrenia or allied types of mental disorder, ranging in age from 25 to 52 years, the average age of the group being 40 years. There were 49 patients in our group, and of these 30 were at one time or another under the personal observation of the writer, while the others were being specifically observed by other physicians who were temporarily assigned to the hypoglycemic ward for six-week periods. The patients under discussion have undergone hypoglycemic treatments for periods ranging from 20 to 85 days. Since with but two exceptions (B V D and G W) our patients were world war veterans, they were as a group considerably older than those being treated in other neuropsychiatric institutions (such as

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state and city psychopathic hospitals) Also their psychoses were of much longer duration than is the rule in younger groups of patients, usually having been manifest for between 15 and 20 years However, we have no reason to believe that the physiological changes we shall discuss are not equally valid for younger groups of patients, especially since on our visits to other institutions where younger patients, both male and female, were being treated, we have frequently observed similar physical findings All our patients had been thoroughly examined before the institution of insulin treatment from the physical, roentgenologic and electrocardiographic angles and presented no prior evidence of definite disease or abnormality of the cardiovascular system

In order to achieve a systematic presentation of our subject we shall consider our data under the usual headings of physical findings, roentgen-ray, and electrocardiographic changes

It is particularly worthy of note that the changes which we consider characteristic of the insulin effect may appear as early as one hour and 17 minutes after the first intramuscular injection of 10 units of insulin (see table 1, G W, case 39)

PART I PHYSICAL FINDINGS

A Review of Literature Apparently the first careful study of the circulation in humans during the hypoglycemic state (arising spontaneously or experimentally produced), was made by Weichmann and Koch¹ in 1928 Their conclusions merit quoting at some length

“(1) In the hypoglycemic attack after insulin injection the venous blood on withdrawal from the unobstructed (i.e. by a tourniquet) cubital vein is strikingly light red Often the arterial and venous blood are indistinguishable One gains the impression not only that ‘arterial’ blood flows out of the vein, but also that it flows out under an increased pressure, that is, it spurts out The bleeding from the point of puncture of the vein is more difficult to stop than is usually the case One feels that one can see the arterial pulse pounding through to the venous side The medium erythrocyte diameter of the venous blood approaches closely that of the arterial blood This finding is explained through a relaxation of the vascular tone The vascular channels open themselves to an extraordinary extent and as a consequence the blood flows more rapidly An increase of the minute volume is to be assumed from this

“(2) In 13 cases which were examined in the hypoglycemic state an acceleration of the pulse could be noted, in two cases the pulse frequency was unchanged, in three cases it was slow A parallelism between the eventual pulse quickening and the status of the blood sugar level was lacking throughout Often the pulse frequency reached the maximum of its acceleration only after the taking on of nourishment, when the blood sugar value had already returned to normal The cause of the pulse frequency can therefore not be attributed to the hypoglycemia as such

TABLE I

Initials Case No	Blood Pressure Before Insulin Treat- ment	Day of Treat- ment	OBSERVATIONS MADE DURING INSULIN TREATMENT					OBSERVATIONS MADE AFTER INSULIN TREATMENT		
			Dose of Insulin	Given at	Clinical Findings	Blood Pressure	Time of Reading	Number of Days Since Last Treat- ment	Clinical Findings	Blood Pressure
C W 10	132/90	69th	180 units	7 06 a m	No definite murmurs	110/76	7 34 a m	40 days	No murmurs	126/76
					Moderate to and fro aor- tic murmurs, pistol shot at brachial	144/0	9 30 a m			
W C 2	128/80	55th	140 units	7 20 a m	Marked to and fro aortic murmur	128/56	8 02 a m	14 days	No murmurs	132/74
					Marked to and fro aortic murmur, loud pistol shot at brachial	150/58	9 16 a m	40 days	No murmurs	146/78
H B 22	125/90	56th	160 units	7 15 a m	Moderate to and fro aor- tic murmur Corrigan pulse, marked to and fro aortic mur- mur, capillary pulsa- tion, pistol shot at brachial	118/56 162/0	7 50 a m 9 20 a m	65 days	No murmurs	138/75
		26th	40 units	7 22 a m	No murmurs	96/60	7 05 a m (before insulin injection)	7 days	Moderate to and fro aortic murmur, slight capillary pulsation, bounding pulse	122/54
		28th	80 units	7 18 a m	Moderate to and fro aor- tic murmurs	116/56	10 30 a m	34 days	No murmurs	118/72
		35th	170 units	7 08 a m	Moderate to and fro aor- tic murmurs	106/56	7 32 a m	59 days	No murmurs	110/66

TABLE I (Continued)

Initials Case No	Blood Pressure Before Insulin Treat- ment	Day of Treat- ment	OBSERVATIONS MADE DURING INSULIN TREATMENT					OBSERVATIONS MADE AFTER INSULIN TREATMENT		
			Dose of Insulin	Given at	Clinical Findings	Blood Pressure	Time of Reading	Number of Days Since Last Treat- ment	Clinical Findings	Blood Pressure
B V D 4	125/80	66th	140 units	7 23 a m	No murmurs	118/82	8 13 a m	7 days	Marked to and fro aortic murmur, bounding pulse, slight capillary pulsation	144/84
			160 units	6 35 a m	Definite to and fro aor- tic murmur	130/56	10 10 a m	59 days	Soft systolic murmur at pulmonic area	134/70
		36th	330 units	7 21 a m	No murmurs	115/70	8 07 a m		Treatment still going on	
		54th	170 units	6 36 a m	Moderate to and fro aor- tic murmurs	134/54	8 46 a m			
		65th	130 units	6 45 a m	Moderate to and fro aor- tic murmur	122/72	2 p m			
G W 39	115/70	1st	10 units	6 41 a m	Soft to and fro aortic murmur	106/0	7 57 a m		Treatment still going on	
					No murmurs	102/68	8 a m			
		12th	100 units	6 40 a m	Moderate to and fro aor- tic murmur	126/55	8 46 a m			
		23rd	90 units	6 46 a m	Soft aortic diastolic mur- mur	112/78	2 p m			
B H 7	94/60	53rd	110 units	7 19 a m	Marked to and fro aor- tic murmur	116/0	7 a m	61 days	Moderate to and fro aortic murmur	108/80
					No definite murmur	116/70	2 45 p m	105 days	Moderate to and fro aortic murmur	146/92

" (3) In the great majority of cases the systolic as well as the diastolic pressure sinks in the hypoglycemic state. In a number of cases, the diastolic pressure sank even more than the systolic. The pulse pressure increased. Since all these changes were not only limited by the hypoglycemic state, but also often remained after the ingestion of food, it is justifiable to assume that they are not merely the result of the lowered blood sugar level, but also of the insulin action per se. Among conditions which can play a rôle in the development of this hypotension associated with hypoglycemia are discussed disturbances in myocardial function, diminution of the total blood volume, diminution of the blood viscosity, and abnormal changes in diameter of the small and smallest blood vessels.

" (4) In the hypoglycemic attack there can be heard transitory aortic diastolic murmurs. In four cases during the hypoglycemic attack, a definite diastolic murmur was audible over the aortic area, which later again disappeared, and was not to be heard in the fasting state. The pulse was *celer*. The blood pressures in these cases were respectively, fasting—125/68, 145/80, 118/69, and 236/111. In the hypoglycemic attack we found them 125/35, 115/40, 122/36, and 207/73. On percussion, the heart seemed to be enlarged to the left."

In their work published in 1929, Lauter and Baumann⁴ in the main confirm the observations of Weichmann and Koch. They again point out that the minute volume is increased in the hypoglycemic state. They add the significant finding that this increase begins even before the obvious clinical symptoms of hypoglycemia appear, and only subsides several hours after the administration of carbohydrate. They further point out that although the venous blood in many cases is strikingly bright red, and shows a smaller oxygen deficit than in the normal, still the oxygen utilization is not at all diminished but either normal or increased. This they explain on the basis of the increased velocity of the blood flow.

Later writers do not seem to have added much that is significant to the above descriptions. Of course, Sakel⁵ and his co-workers have noted the appearance of tachycardia, bradycardia, indeterminate arrhythmias and increased pulse pressures, and have delimited rather arbitrarily the "safe" limits for their fluctuation during the insulin treatment for schizophrenia. On the other hand, we find the following statement in Hadorn's paper⁶ published in September, 1936, based on the examination of 31 patients undergoing the shock treatment: "The percussion and auscultatory findings showed no change after insulin, except for frequency and rhythm changes."

B Clinical Observations Under Insulin Shock Treatment In comparing the following observations with those made by Weichmann and Koch, etc., the differences between therapeutic insulin hypoglycemia, and the experimental hypoglycemias produced and observed by the earlier authors must be borne in mind. In the first place experimental hypoglycemias were rarely maintained more than an hour or two at the most, while therapeutic

hypoglycemia is routinely maintained for four or five hours or longer, in the second place, experimental hypoglycemias were rarely repeated more than a couple of times in the same individual subjects, while therapeutic hypoglycemia has been induced repeatedly for weeks and months in individual schizophrenic patients. In fact one of our patients had been treated with relatively large doses of insulin for 85 treatment days. Consequently, it is but to be expected that more frequent, more constant, more profound, and perhaps more lasting cardiovascular changes will be found in the latter instances.

From our own experience and observations we have derived the following picture of the patients' state under therapeutic hypoglycemia. We find it convenient to divide the vascular physical findings into two groups: those attributable directly to variations in the vasomotor tonus, and those attributable directly to changes in the cardio-aortic region itself. Within a few minutes after the intramuscular injection of insulin in effective doses there begin to appear vascular evidences of altered activity of the vegetative nervous system, in the sense of varying degrees of balance between the sympathetic and parasympathetic activity. On inspection, the *color* of patients shows marked variations. Some show a facial flush of fluctuating intensity throughout the course of (as well as after) the hypoglycemia. Others show predominantly a pallor during the course of the hypoglycemia. Others show comparatively little alterations from their usual appearance. The majority of cases show an intermediate degree of intensity of flushing and fluctuations between flush and pallor. The flushing usually shows marked regional variations, usually being most pronounced in the head and neck, and in most cases also involving the hands and feet. In the *typical* case the flush predominates in the pre-comatose (drowsy, somnolent) stage, and in the stage of light coma (muscular tonicity, extensor spasms, involuntary stereotyped movements, excitement), while pallor predominates in the stage of deep coma (muscular relaxation, absent corneals, positive Babinski's). After termination normal or ruddy facies are again the rule. Of course, cyanosis develops whenever there is interference with respiration due to convulsive or prolonged tonic reactions, accumulation of mucus in the air passages, etc. Since many patients show spontaneous fluctuations in the depth of their coma, they usually show corresponding changes in color. Often, we have observed the development of a circumoral, nasal, and circumnasal pallor, which gives the patient a "drawn" appearance suggesting the hippocratic facies. In one case (C.C.), we have observed repeatedly a "butterfly" flush involving symmetrically both cheeks and the middle region of the forehead, while the nose itself and circumoral region and remainder of the face had the usual pallor.

As regards changes occurring in the cardio-aortic region itself we have found symptoms and signs presenting themselves, which undoubtedly are the effects of a *varying* and *variable* degree of dilatation in the region of the aortic bulb and ascending aorta. On inspection we quite regularly see an

increased degree of peripheral vascular pulsation. An increased venous pulsation in the neck is also usually evident. Along with this we find that the pulse assumes a "bounding" character, and associated with this we find an increasing pulse pressure chiefly dependent upon a drop in the diastolic blood pressure. As the diastolic pressure drops further and often ultimately reaches zero the pulse assumes a definite "Corrigan" character. When this occurs we usually can hear a "pistol shot" sound over the brachial artery and at times a "Duroziez" murmur over the femoral artery. Occasionally even a capillary pulsation becomes apparent. On a few occasions when the above phenomena were most pronounced, we have felt a systolic thrill over the brachial artery. With careful auscultation we can usually make out a to and fro murmur which seems to originate over the aortic region and is transmitted down the left border of the sternum and out towards the apex. The systolic component of the murmur is usually most evident, while the diastolic component varies from the faintest whiff accompanying the second sound, to a fairly well defined aortic regurgitant murmur. In some cases (particularly when the *systolic* pressure remains unusually low), we can only make out a single sound at the base, suggesting that there is insufficient impact against the semilunar valves or such a degree of insufficiency, as to produce no audible second sound. From such findings we may surmise that there is also associated with the aortic dilatation, a similar dilatation of the pulmonic conus. These findings, we must repeat, are found to be present to a variable degree in different patients, and in the same patient. However, they may appear very soon after the injection of insulin, and even after the first dose. Thus, with patient 39, G. W., a blood pressure of 106/0 was obtained one hour and 16 minutes after the first injection of ten units of insulin, while three minutes later the reading was 102/68. In perhaps 30 per cent of our patients the aortic dilatation phenomena were readily detectable on almost any occasion, after the treatment was well established. In the others the more evanescent character of the phenomena was demonstrated by the fact that they were found only occasionally, and only because these patients were examined day after day during various phases of the treatment. Thus, in personally following a series of 16 cases under intensive treatment for a period of six weeks, the writer was able to detect the findings of aortic dilatation at one time or another, in all but one case. In most of these cases, these phenomena persisted for various periods of time after the termination of the hypoglycemia, but invariably the findings were less marked the longer the time interval between the last hypoglycemic period and the date of observation. As a rule, the abnormal pulse pressures showed the recession to the normal levels first, while the murmurs persisted for a considerably longer period. In the accompanying table 1, we have indicated certain of the more typical clinical findings in individual cases. Sufficient data are given there to show that the findings in any specific case at any particular time are entirely unpredictable. The phenomena of aortic dilatation may be either evident or absent, whether in the morning before the insulin

injection has been given, or in the afternoon several hours after termination, or during the various phases of hypoglycemic shock, and finally these phenomena in some cases may persist for several months after the use of insulin has been discontinued (see figures on case 7, B H). However, as a rule the aortic dilatation phenomena show a progressive diminution in intensity as time goes on.

The question of pulse frequency and rhythm during the hypoglycemic shock treatment has been thoroughly covered by previous writers. Our observations are essentially in agreement with these previous reports. We have found usually a slight progressive acceleration of the pulse rate during the somnolent and excitement stages (stage of light shock), with a tendency to relative slowing during the stage of deep shock, and again a tendency towards moderate acceleration for a couple of hours after termination. Only very rarely have we observed tachycardias above 130 or bradycardias below 50. The rhythm is usually grossly regular, the only abnormality fairly frequently observed being a sinus arrhythmia. Occasionally, infrequent extrasystoles have appeared,—but we have not observed any more serious disturbances in rhythm in any of our patients.

In seeking for a physiological explanation of the cardiovascular changes, particularly the aortic dilatation phenomena during the hypoglycemic treatment, we have found the following material which illuminates this question. It has long been known that insulin hypoglycemia calls forth a physiological outpouring of adrenalin into the blood stream. Brandt and Katz² in 1933, proved directly the existence of this compensatory adrenalinemia by biological and chemical tests. In one of their typical case protocols they show that the maximum adrenalin effect appeared 34 minutes after the intravenous injection of 30 units of crystalline insulin. Meythaler⁷ in 1935, showed that compensatory adrenalinemia appears after the intravenous injection of small doses (a few units) of insulin, long before the blood sugar level has reached the critical so-called hypoglycemic range. That is, that with every *decline* of the blood sugar level in the blood, regardless of the original level, the adrenalin output is increased. This finding, of course, explains why the symptoms of adrenalin activity appear so soon after the insulin injection, even while the blood sugar level is still fairly normal. An explanation of the actual aortic dilatation phenomena is then found in the work of J. Gottesman and J. Pal⁸ as described in the latter's paper in 1935. These workers showed that within three to eight minutes after the subcutaneous injection of 0.001 gm. adrenalin there appeared *pulsus celer* and *altus*, a diastolic pressure of zero, and the typical murmurs, all of which they state are due to an active widening of the ascending aorta. This change, Pal asserts, is a regular manifestation of the stimulation of the sympathetic innervation of the cardio-aortic region. The bradycardia usually seen during the phase of "deep" shock is also attributable to adrenalinemia, as the cardio-inhibitory function of adrenalin (operating via the vagus), is well established.⁹

Reasoning conversely from the above facts, the inference may be made that as long as aortic dilatation phenomena persist in any individual case, an adrenalinemia very likely remains associated with them. It is particularly important to establish this point since our clinical studies have shown that the aortic dilatation phenomena may persist for weeks and even months after the completion of the hypoglycemic treatment. It is our purpose in subsequent studies to determine directly the extent of persistence of adrenalinemia.

Since insulin has been known to precipitate coronary attacks in cardiac patients^{10, 11} and moreover since S. A. Levine has proposed the use of the "adrenalin test" for distinguishing between true and pseudo-angina pectoris, does not this view of the cardio-aortic changes during the hypoglycemic treatment indicate that we are exposing our patients to an excessive danger of cardiac accidents? To this question we can answer by stating that experience has shown that no such danger is present in properly selected cases. Our own experience particularly bears this out, since we have dealt with a group of patients whose average age is 40 years, and still have had no untoward cardiac complications. As long as Dr. Sakel's list of contraindications for his treatment are borne in mind, we feel one should have no undue apprehension on this account.

PART II ROENTGEN-RAY FINDINGS

A survey of the literature available at this time indicates that hitherto no attempts have been made to follow the cardiac changes during the hypoglycemic treatment, with the roentgen-ray. This is not surprising when one considers the practical difficulties which one encounters in attempting to secure roentgenograms of the heart at different times under sufficiently fixed conditions so that the measurements may be compared with a reasonable degree of accuracy. In order to achieve this purpose, it is above all necessary to have fairly cooperative patients who will at least make an attempt to hold their breath at deep inspiration during the period of exposure. Such suitable cooperation is especially difficult to obtain with psychotic patients. To eliminate as far as possible the error due to this factor, we selected for this study 10 patients, who, we felt, would cooperate best during the taking of the roentgen-ray picture. On these patients a total of 26 standard six-foot flat heart plates were taken. Films were taken before, during, and after the course of hypoglycemic treatment. Unfortunately, no films could be taken during the actual hypoglycemic state, since it was impracticable to transport patients during hypoglycemic shock, and since our portable roentgen-ray apparatus could not be adapted to take sufficiently accurate six foot heart plates. Consequently, it must be borne in mind, that those plates listed as being taken "during the course" of the hypoglycemic treatment were actually taken while the patients were on an ambulatory status, i. e., in the afternoon after termination or on a rest day. As a check on the standardization of conditions under which films to be com-

pared were taken, we decided on the following criteria first, the trans-thoracic diameter in each film was to vary not more than five millimeters from the film with which it was to be compared, second, the level of the diaphragm in films which were to be compared had to be essentially similar. Because of the strict adherence to these criteria, we found it necessary to eliminate 12 of the 26 films from our study. However, because of these precautions the margin of technical error involved in our method is reduced to a theoretical 2 per cent. Consequently, any difference in measurements greater than 2 per cent may be considered significant as regards actual physical change. The results of our studies on the 14 films (taken on six different patients), which were suitable for comparison, are listed in table 2. Wherever possible (as in cases 2, 7, and 22), the total transverse measurement of the aortic arch was used as an indicator of the changes occurring at the base of the heart. In the three other cases this measurement could not be used because the right border of the aortic arch could not be clearly defined, inasmuch as it was transposed over the dense shadow of the vertebral bodies. Consequently, in these cases we used the "Upper Left Margin" measurement as defined in the table.

Table 2 shows that in all cases in which comparable films were available, a significant increase in the diameters of the heart appears during the insulin treatment, and evidently may persist for at least two months after the conclusion of the prolonged course of treatment. The increase is evidently more marked in the basal region of the heart than in the apical region of the heart (the figures ranging from +4 per cent to +24 per cent in the former case, as compared to figures of 0 to +14 per cent in the latter case).

Although the measurements given above indicate a distinct increase in the cardiac diameters, in no case do they reach values that are ordinarily considered pathological (viz aortic arch measurements exceeding 8 centimeters, or a cardio-thoracic ratio exceeding $\frac{1}{2}$). All in all the roentgen-ray changes thus far found coincide fairly well with the physical changes described in Part I of this paper.

PART III ELECTROCARDIOGRAPHIC FINDINGS

Perhaps more has been done in the way of electrocardiographic studies during hypoglycemia, than in any other phase of this problem. Before the introduction of the Sakel treatment, numerous reports appeared describing the changes occurring in hypoglycemic attacks in diabetics as well as in experimental hypoglycemias. An excellent summary of this early work is found in the paper of Romano, Mazzei and Baila,³ who in addition report their own careful observations on 30 normal subjects given 15 units of insulin intravenously. The earlier reports agree substantially in reporting most frequently "T"-wave changes in the way of flattening or inversion. In addition, mention is made in the individual reports of P-wave changes, widening of the QRS complex, and occasionally disturbances in rhythm.

TABLE 11

Roentgen-Ray Studies

Initials	Total Number of Treatments	Röntgen ray Findings Before Treatment	Date	Röntgen-ray Findings During Treatment	Date	% Change	Röntgen-ray Findings After Treatment	Date	% Change	Remarks
B V D 4	85 8-13-37	ULM = 4.8 cm CT = $\frac{12.5}{33.2}$ cm	2-16-37	None available			ULM = 5.6 cm CT = $\frac{14.3}{32.8}$ cm	9-27-37	+17% +14%	
							ULM = 5 cm CT = $\frac{13.6}{33.3}$ cm	10-11-37	+4% +9%	
W C 2	75 8-6-37	AA = 6.5 cm CT = $\frac{12.4}{30.6}$ cm	1-14-37	AA = 7 cm CT = $\frac{13.3}{30.6}$ cm	7-12-37	+8% +7%	None available			
B H 7	54 6-26-37	AA = 5.7 cm CT = $\frac{12.1}{30}$ cm	2-25-37	None available			AA = 6 cm CT = $\frac{12.2}{29.8}$ cm	9-2-37	+5% no significant change	
H B 22	50 8-13-37	AA = 4.7 cm CT = $\frac{11.5}{30.6}$ cm	3-23-37	None available			AA = 5.1 cm CT = $\frac{12}{30.7}$ cm	9-1-37	+8% +4%	Between the dates of these two roentgen rays the patient was placed on ground pirole and was permitted considerably more physical activity. This may be a factor in the progressive increase in cardiac measurements after treatment was terminated
							AA = 5.4 cm CT = $\frac{12.2}{30.7}$ cm	10-12-37	+15% +6%	
T M 21	being continued	ULM = 5 cm CT = $\frac{12}{30.2}$ cm	1-13-37	ULM = 6.2 cm CT = $\frac{12.3}{30.3}$ cm	9-2-37	+24% +24%	Treatment being continued			
P N 25	62 8-12-37	ULM = 4.7 cm CT = $\frac{10.9}{27.8}$ cm	3-4-37	None available			ULM = 5.2 cm CT = $\frac{12}{28}$ cm	10-12-37	+11% +10%	

Glossary ULM = Upper left margin measurement (always taken at lower border of third intercostal space)

AA = Aortic arch measurement (total)—(always taken at lower border of second intercostal space)

CT = Cardio-Thoracic Ratio measurements, consisting of the $\frac{\text{Transverse Diam. of the Heart}}{\text{Transverse Chest Diameter}}$

such as bradycardia, alternation, auricular and ventricular extrasystoles, sinus arrhythmia, and exceptionally, disturbances in conduction. Some writers also mention changes in voltage (usually increase), of the R- and S-waves.

Romano and his co-workers reporting on their own material of 30 cases noted

- (1) Increased frequency in 83 per cent of their cases
- (2) Increased voltage of the P-wave in three cases, diminution in one case, inversion in one case
- (3) Increased voltage of R_2 and R_3 six times, increase of S_2 in two cases and diminution of S_3 in two cases
- (4) Appearance of a small "U"-wave on two occasions
- (5) Diminution of the height of the "T"-wave in 27 of the 30 cases (This includes negativity in many instances)

They particularly point out that in spite of the fact that these alterations were in many cases quite definite, they did not produce any angina pectoris or phenomena of cardiac decompensation in any of their healthy subjects.

DeChatel and Palisa,¹² working in Sakel's clinic, on 19 schizophrenic patients undergoing the hypoglycemic treatment, noted invariably that "T"-wave changes occurred consisting of lowering of the "T"-wave, and in all cases definite inversion in Lead IV. In two cases they observed a very marked sinus arrhythmia, but no other disturbances of conduction. They found that the electrocardiographic changes were most evident after 45 minutes from the time of injection of the insulin, and persisted until perhaps one-half to one hour after the termination of the coma.

W. Hadorn⁹ of Bern, Switzerland, studied 31 patients undergoing the hypoglycemic shock treatment and found significant electrocardiographic changes in almost two-thirds of these cases. These consisted of arrhythmias of minor significance, lowering of ST, flattening and sometimes negativity of the T-wave, widening of the QRS, and occasional appearance of U-waves. He too finds that these changes are usually reversible.

Our own limited experience agrees quite closely with the findings of these previous workers. We took 12 electrocardiograms during the course of treatment which could be compared with graphs taken just before the beginning of treatment. We noted no P-wave changes, an increase of Q_3 in two instances, an increase in R voltage in four instances, a diminution in R voltage in two instances, lowering of the T-wave in two instances, negativity of T_2 and T_3 in two instances, increased voltage of T-wave in one instance (graph taken on a rest day), marked sinus arrhythmia in two instances, infrequent left ventricular extrasystoles in one instance, slight widening of the QRS in two instances (from 0.06 sec to 0.08 sec and from 0.08 sec to 0.10 sec respectively). None of the more significant changes, viz., the T-wave negativity and pathological Q_3 , were found in any case except during the phase of shock.

It is generally agreed that the electrocardiographic changes noted above are evidences of states of myocardial mal-nutrition or anoxemia. Obviously, insulin hypoglycemia operates to produce this effect at least in part by removing in large measure the carbohydrate which the heart muscle needs. However, Hadoin⁶ has shown that this is not the only factor, since he was able to produce similar changes in the "T"-waves when he injected glucose intravenously along with the insulin. Also, the persistence of the EKG changes for some hours after the termination of the hypoglycemic state is evidence for the existence of some other cause. This cause is, most likely, again the adrenalin effect, which operates to produce a myocardial ischemia by bringing about the reduction in diastolic pressure which prevents proper filling of the coronary arteries.

SUMMARY

During the course of insulin hypoglycemic treatment profound changes arise in the cardio-vascular system, which have been inadequately described in previous reports regarding this method of therapy.

A review of the literature regarding experimental and spontaneous hypoglycemia shows that most of these changes have been observed from time to time in rare instances. The work of Weichmann and Koch is cited as giving the most comprehensive account of the cardiovascular changes in experimental hypoglycemia. These changes consist of peripheral vasomotor phenomena, which are best explained by variations in the activity of the several parts and regions of the vegetative nervous system, and cardio-aortic phenomena which are best explained as a result of the adrenalinemia produced by the action of insulin. The cardio-aortic changes consist primarily of an active widening of the aortic bulb and ascending aorta which may develop to such a degree as to produce typical symptoms and signs of aortic insufficiency. These changes were all found to be reversible, though they persist for varying periods of time after the termination of experimental hypoglycemia.

Our own work on 49 patients undergoing the Sakel regimen for schizophrenia, proves that essentially similar physiological changes, viz the vasomotor phenomena and the cardio-aortic dilatation phenomena, appear quite regularly at one time or another during the course of this treatment. The persistence of these changes, albeit in a progressively diminishing degree, for weeks and months in certain cases, is also demonstrated. The trend in all cases seems to be towards a reversibility of these cardiovascular changes, so that they may be considered physiological rather than pathological in significance.

Roentgen-ray studies taken during and after the course of the hypoglycemic treatment afford concrete confirmatory evidence of the occurrence of these cardio-aortic changes. These studies demonstrate a relatively greater increase in the basal as compared with the apical diameters of the heart, and in the main, coincide with the clinical physical findings.

Our electrocardiographic studies are in accord with those described by previous authors, notably W Hadoin⁶ and Romano, Mazzei and Baila³. The most frequent electrocardiographic abnormalities in hypoglycemia are seen to be flattening and inversion of T-waves, and sinus arrhythmias. Other changes which have been noted are pathological "Q_s"-waves, changes in R and S voltage, slight widening of the QRS complexes, appearance of "U"-waves, appearance of auricular and ventricular extrasystoles. The theoretical implications of these changes are discussed in the text.

BIBLIOGRAPHY

- 1 WEICHMANN, ERNST and KOCH, FRITZ. The condition of the circulation in the hypoglycemic state, *Deutsch Arch f klin Med*, 1929, clviii, 176.
- 2 BRANDT, F, and KATZ, G. Concerning the evidence of adrenalin secretion in humans. I. Insulin hypoglycemia, *Ztschr f klin Med*, 1933, cxviii, 23-39.
- 3 ROMANO, N, MAZZEI, E S, BAILA, M R. Cardio-vascular disturbances in insulin hypoglycemia, *Revista de la Asociacion Medica Argentina*, 1936, ix, 1175.
- 4 LAUTER, S, and BAUMANN, H. The circulation and respiration in the hypoglycemic state, *Deutsch Arch f klin Med*, 1929, clviii, 161.
- 5 DUSSIK, K T, and SAKEL, M. Results of the hypoglycemic-shock treatment of schizophrenia, *Ztschr f d ges Neurol u Psychiat*, 1936, clv, 351-415.
- 6 HADORN, W. Investigations concerning the effect on the heart of insulin and hypoglycemia, *Ztschr f klin Med*, 1936, cxviii, 643.
- 7 MEYTHALER, F. Investigations of the adrenalin content of the blood with blood sugar variations, *Arch f exper Path u Pharm*, 1935, cxlviii, 130.
- 8 PAL, J. Regarding the cardio-aortic vascular region and angina pectoris, *Klin Wchnschr*, 1935, 1737.
- 9 HOWELL, W. *Textbook of physiology*, 1925, (Ninth Edition), Saunders, Philadelphia, p 882.
- 10 PARSONNET, A E, and HYMAN, A S. Insulin angina, *ANN INT MED*, 1931, iv, 1247.
- 11 TURNER, K B. Insulin shock as the cause of cardiac pain, *Am Heart Jr*, 1930, v, 671.
- 12 DECHATEL, and PALISA, CH. The electrocardiogram in severe hypoglycemic shock, *Klin Wchnschr*, 1935, 1784.

POSSIBILITIES IN BIOLOGICAL ENGINEERING

By KARL T. COMPTON, *Cambridge, Massachusetts*

WHEN I asked myself why I, a physicist, should be invited to address you, America's most distinguished body of physicians, I found an answer extending back over many centuries. For physics and medicine have been closely associated from their very beginnings. The words physics and physician both derive from the Greek root meaning "that which pertains to nature" as distinguished from the spiritual, mental and moral world. Webster's Dictionary gives two definitions of "physicist" first, one versed in medical science, second, one versed in natural science. In France I, as a physicist, would be called a physicien. In Germany I would be a physiker which, in English, is one who administers a physic.

In the early days of science there was little differentiation between the study of animate and inanimate phenomena, the great scientists of the day concerned themselves indiscriminately with medicine, physics and alchemy. But, as knowledge of natural science grew, specialization became necessary in the three great fields of biology, physics and chemistry. Medicine and engineering emerged as combinations of art and applied science, medicine being based largely on biology and engineering on physics.

It has been the history of science that this tendency to specialization and differentiation into different fields is frequently followed by a merging together again. This happens when some fundamental discoveries disclose the underlying unity of two branches of science which had hitherto developed on less fundamental and apparently unrelated bases. The best example of this is in physics and chemistry. A generation ago it was easy to distinguish a physicist from a chemist. One dealt with matter in bulk and the other with changes in molecular constitution. There still exists a difference between what might be called the plumbing type of physics and the culinary type of chemistry, but in their interpretive and many of their operational aspects the two sciences are now completely merged, to their very great advantage.

I think we all believe that there is a basic unity of interpretation and understanding underlying all phenomena of the material world. It is only our ignorance or lack of skill which forces us to proceed along different lines, based on different sets of fundamental laws. With increasing knowledge these barriers break down, and new lines of attack are opened up with new weapons. My purpose, in this address, is to discuss the possibilities of a closer working liaison between the biological, physical and chemical sciences, together with their applied aspects in medicine and engineering.

* Convocation Address, Twenty-Second Annual Session, American College of Physicians, New York, April 6, 1938, by Karl T. Compton, President, Massachusetts Institute of Technology.

The opportunities for such liaison may be illustrated by two examples. Consider the technic of the physician in a clinical examination. He takes the patient's temperature and pulse rate, listens with a stethoscope to his heart and lung action, examines his eyes, nose and throat with optical instruments, takes an electrocardiogram and a series of roentgen-ray photographs. Thus far he uses instruments devised by physicists. He also employs chemical methods in analyses of blood, urine, metabolism and perhaps tests the spinal fluid. If he prescribes a treatment other than diet, rest, exercise or abstinence from tobacco, it is likely to be physical therapy with roentgen-rays, heat or ultraviolet light, or chemical treatment with medicines.

Bone disorders are detected and observed by roentgen-rays. The processes of bone metabolism are affected by diet, by glandular action stimulated by chemical hormones like parathormone and by ultraviolet light. The exact operation of these processes may be studied by use of chemical isotopes or radioactive chemicals produced and detected by physical methods and used as tracers. If we wish, for example, to study in detail the body process between the drinking of water and its effect, if any, on the joints, we could give the patient a little "heavy water," containing deuterium instead of hydrogen, and trace this deuterium as it proceeds in metabolism to the various fluids and tissues of the body. Or, similarly, we can produce artificial radioactive calcium or phosphorus by the modern alchemy possible with proper use of very high voltage equipment, feed this calcium or phosphorus in food to the patient or experimental animal, finally detect quantitatively and with marvelous sensitiveness the rate at which this material deposits in the bones, with aid of physical instruments which were originally devised for experiments on cosmic rays and for measuring the geological age of rocks.

These two illustrations, chosen from the field of medicine, could be matched by many others from the allied life sciences comprised under the general head of biology. For example, the physical agent roentgen-rays and the chemical agent calcodine have opened up entirely new vistas in genetics. Bacteriology and mechanical engineering are revolutionizing the food processing industries. We now have yeast and mould cells being bombarded by electrons in vacuum tubes, brain actions being detected by radio amplifying apparatus, human tissues being measured by electrical engineering methods to discover their "phase angle" under different conditions, gonorrhea cured by electrical heating methods which were developed for metallurgical uses, biological membranes partially simulated by chemically produced films.

I recall some ten years ago the late Dr. Augustus Trowbridge, then European Director for the Natural Sciences under the International Education Board, told me of his belief, based on study of work in many laboratories, that the next generation would witness a fundamental forward movement in the biological sciences comparable to that which came in the

physical sciences with the work of Faraday and Maxwell, or more recently with the discoveries of the electron, Roentgen-rays, radioactivity and atomic transmutation. He said, furthermore, that he expected this advance in biology to come about through use of techniques supplied from the sister sciences of physics and chemistry. Certainly the new developments of the intervening ten years go far in substantiation of this prophecy.

Admitting, therefore, the rapid advance of biological science and its opportunities to draw for assistance upon its sister sciences, the question arises, is there some step which we can now take that will facilitate and expedite this development? I believe that one clue to the answer to this question is found in two parallel situations. Very, very few biologists or physicians are trained in these techniques of physics and chemistry, or have any understanding of the concepts and methods of these sciences which may be applicable in their own science, conversely very, very few physicists or chemists have any knowledge of the problems of biology. Neither speaks the other's language or thinks about his problems. So, I believe that one forward-looking step may be taken by the parallel training of young scientists in biology, physics and chemistry in a manner which I will suggest later.

Of course this is not a new idea. There are some biophysicists and some biochemists who are doing excellent work. And for many years the border lines between the biology and physics and biology and chemistry have been attacked. But these have been reconnaissance skirmishes by raiding parties rather than a major engagement by an adequate and well equipped army. I know that most physicists who have gone into biophysics have gone in mainly as technicians, while most biologists in the same field have been fumbling with big ideas which they had not the background to handle effectively. Those few who have become first-rate biophysicists or biochemists have done so through unusual native ability and hard work, and not through adequate training.

Such considerations led a group of my colleagues, who were interested in attempting to devise an improved basic training for the fields of biophysics and biochemistry, to follow a suggestion derived from a somewhat analogous situation about 30 years ago—that time in the field of chemistry rather than biology. Then industrial chemistry was rapidly becoming important. Many successful exploratory developments had been carried out in applying methods and principles of physics and mechanical engineering to chemical manufacture. At that point, three men together devised a new type of training for young men preparing for the chemical manufacturing industry. Instead of cramming the minds of student chemists with a mass of descriptive detail as to how this product is manufactured, that product is manufactured, and so on, they concentrated their training on a limited number of processes and operations which were basic to all chemical manufacture, and gave a thorough grasp of these processes from the physical, chemical and mathematical viewpoints—all built upon thorough groundwork in these basic sciences. These unit operations were things like distillation, mixing,

drying, heat transfer, chemical reaction, transfer of fluids, etc. At one stroke this new concept brought order out of chaos in the chemical industries, their problems had been reduced to common terms, technical advance in one industry was immediately transferable to other industries. In the short space of 30 years chemical engineering has become one of the most useful and vigorous of all the applied sciences.

Just as systematic applications of physics and mechanical engineering to chemistry produced a useful art of chemical engineering, so a systematic application to biology of physics, chemistry and electrical engineering may create a useful art of biological engineering. The choice of the name "biological engineering" is the result of much thought and consultation. The names biophysics and biochemistry are, neither of them, sufficiently inclusive, and their combination is clumsy. Biotechnology would be a good title. But the designation of biological engineering was suggested as appropriate because our objective so aptly conforms to the well known definition of engineering as "the art of organizing and directing men and of controlling the forces and materials of nature for the benefit of the human race." Within this conception lies ample scope for every activity from instrumentation to theory, from biophysics to biochemistry, so long as its objective is the marshalling of all available resources to aid biology for the benefit of humanity. When one of my colleagues first suggested this name to me, he said, "I know you don't like the name now, but it will grow on you as you think it over." He was right.

What, then, is the program for biological engineering, in order that it may fulfill its objective of systematically uniting physics, chemistry, mathematics and engineering to serve biology? As I see it, three features are essential: an educational program, a research program and an organization. Realizing that, if the program has merit, it will be improved by experience and further thought, nevertheless the following suggestions may be offered as a starting point.

Educational Program The first consideration in planning an educational program is its objective and then its scope and subject matter. Here we may follow the analogy of chemical engineering, with its "unit processes" and "unit operations," and proceed to analyze our available concepts, tools, technics and opportunities, as follows.

Among the types of energy likely to be usable are the following: electromagnetic vibrations—infra-red, visible and ultraviolet light, roentgen-rays, radio frequencies, radioactivity, electricity, bombarding particles like electrons, protons or neutrons, supersonic vibrations, heat, chemical energy, magnetic fields, surface tension.

Among the ways in which these types of energy are likely to be involved are the following: stimulation of protoplasts, induced chemical changes in organic materials, living or once living, effects on enzyme action, therapy in disease, abiotic action on deleterious microorganisms, effects on hormones.

and vitamins, spectroscopic analyses, roentgen-ray analyses of crystal structure or molecular aggregations, electiokinetics of cell membranes, electrophoresis of cells, tracer studies in metabolism and other physiological processes, mutations

There will be required the construction and operation of devices for objective measurement of the changes induced as above, including measuring and recording of temperature, pressure, humidity, air motion, gaseous relations, motion and time, amplification of feeble energies without distortion, by mechanical, thermionic or photronic devices, radiation measurements, as roentgen-ray dosages, radioactivity, cosmic ray counting, mitogenic radiations, spectrophotometry, hydrogen-ion concentrations, oxidation-reduction potentials, vapor pressures, heat flow and insulation thermodynamics, surface tension, conductance and impedance in protoplasts, diffusion and osmotic effects across membranes, molecular weights and isoelectric points, colloidal phenomena, agglutination and anti-body relations, electrical potentials, Donnan equilibria and Helmholtz double layer phenomena, axone potentials and action currents, reflex time and tropisms

Among the technical skills useful in constructing experimental and recording apparatus the following are suggested design and construction of amplifier circuits, transformers and meters, machine tool work and glass blowing, design and operation of vacuum pumps and pressure gauges, production of uniform or varying temperatures, design and operation of thermionic, photronic, vacuum and ionization tubes, photography and photometry, optical measurements, spectroscopy, absorption and emission spectra, absorption coefficients, use of glass, quartz and grating spectrometers, supersonic devices, radiation sources, electromagnetic, monochromatic, etc., use of optical filters, microscopic technics, including transmitted and oblique illumination, dark field, quartz and lithium fluoride microscopes, ultramicroscopes, preparation and handling of pure gases, equipment for organic and inorganic chemical analyses, centrifuges

Among the fields of usefulness of biological engineers may be listed medical schools, hospitals, medical and biological institutes, universities, food companies, as packers, canners, bakers, shippers and dairy products, manufacturers of pharmaceutical instruments, chemicals or drugs, industrial hygiene activities, government laboratories, as agriculture, food, health and standards

On the basis of this analysis, the next step is to devise an educational curriculum which will provide knowledge of biology and at the same time training in the principles and technics of the cooperating sciences as listed above. I believe that this curriculum should recognize first, that the field is too broad to be handled, even in an introductory manner, in a four year college course, and second, that education along these various lines should proceed more or less in parallel rather than *ad seriatim*.

This fact of "parallel" training is important. A student entering this field has hitherto been quite generally forced to specialize in one aspect, such

as chemistry or biology, and has then had to go back after graduation to pick up the remaining features of the combined program. As I have seen this attempted in a number of cases, I have been impressed with its poor psychological arrangement. But the curriculum which I shall describe makes progress possible at a more or less uniform level in the various fields. This has the advantage of breaking down the more or less artificial barriers between the different fields and of permitting a more unified conception and a more coordinated training.

Along these lines, therefore, the following curriculum of professional subjects has been approved by the faculty of the Massachusetts Institute of Technology for a course in Biological Engineering.

First year general chemistry, physics and calculus, each through the year, engineering drawing and descriptive geometry each for a half year.

Second year physics through the year, and a half year each of general chemistry, qualitative analysis, general biology, comparative anatomy, calculus and differential equations.

Ensuing summer organic chemistry.

Third year physical chemistry through the year, and a half year each of invertebrate zoology, bacteriology, physiology and electrical engineering.

Fourth year a half year each of electrical engineering, biochemistry, biophysics, optics, atomic structure and some professional electives.

Fifth year advanced bacteriology, colloid chemistry, biological engineering and thesis through the year, and a half year of zymology and some professional electives.

In addition to these professional subjects, the curriculum includes courses in English, history, modern language, economics and some elective general studies.

The professional electives are chosen in the fields of physics, chemistry, biology or engineering.

This five year course leads to a master's degree in biological engineering, but students with promise and ambition should be urged to proceed with at least two more years of graduate study to the doctorate.

Research Program I believe that the best possible value in this field of biological engineering can only be attained if a research program and an educational program proceed side by side, each drawing strength and inspiration from the other. It is obviously not possible here to outline the scope and content of a research program, since this will vary greatly in accordance with the interests of the staff. You may be interested, however, in a very brief description of what we are now doing in this field at the Massachusetts Institute of Technology—not as a statement of an ideal, but rather as an illustration of the opportunities for cooperation between specialists in different departments drawn together around biological engineering as a coordinating influence. Associated in many aspects of this

work are also the Harvard Medical School, the Massachusetts General Hospital, the Lahey Clinic and other groups, for such a program must be essentially cooperative

The technic of radioactivity measurement developed by Professor Evans has been combined with that of the metabolism of calcium and allied metals under Professor Aub to perfect a method for measurement and cure of radium poisoning. Similar radioactivity technics are being used in cooperation with Dr Hertz working under Dr Means to investigate iodine metabolism with some interesting therapeutic possibilities in view. Also this radioactive technic is being used to investigate phosphorus metabolism in the dentine and enamel of the teeth of humans and rodents, in the study of bone sarcoma, and other problems.

The high voltage electrostatic generator invented by Professor Van de Graaff is in successful use in a 1,200,000 volt roentgen-ray installation in the Huntington Memorial Hospital under Dr Dresser, who recently reported the very promising clinical results on different types of cancer in the first six months of use. An improved model of this type of roentgen-ray outfit is now under construction in our electrical engineering laboratories for the Massachusetts General Hospital. The super voltage Van de Graaff generator, formerly installed on the estate of Colonel Green at Round Hill, has been moved to Cambridge and is being adapted for the production of large quantities of artificial radioactive materials, like sodium, iodine or phosphorus, for use in physiological and medical research.

The fundamental nature of the biological action of penetrating radiations is being investigated, starting with a very simple case—the bombardment of unicellular organisms by electrons of regulated speeds.

A series of organic peroxides has been discovered by Professor Milas, possessing biologically interesting properties. For example, they are unusually good bactericides and fungicides, and have yielded some remarkable results in the cure of athlete's foot and pyorrhea. Their mild oxidizing properties, and relative absence of deleterious action on tissues, suggests their possible beneficial action in diseases, like cancer and dementia praecox, which are characterized by low oxygen metabolism. Investigation of these possibilities is being undertaken in collaboration with Dr Hoskins, Director of the Memorial Foundation for Neuro-Endocrine Research.

Cooperation of physicists with Professor Bunker has led to invention of a new method for activating ergosterol and also to a technic of monochromatic ultraviolet irradiation which has permitted a closer definition of the spectral range and efficiencies of antirachitic effects of ultraviolet light.

An automatic quantitative color analyzer, developed by Professor Hardy, is being used to separate the reddening of skin due to modified vascular action from true erythema produced by roentgen-rays and other agencies.

The carcinogenic properties of chemicals are being studied by a new method by Dr Goldstein. He finds that those chemicals which will produce cancer in experimental animals after some months of application, will also

produce abnormal growths in bacteria in only a few hours. Thus far he has found complete agreement as to carcinogenic or noncarcinogenic properties of the various chemicals tried, and if this agreement is found to be general, the new bacterial test will greatly expedite the examination of other chemicals with respect to this property.

Utilization of facilities for upper atmosphere studies provided by our meteorological department has enabled Professor Proctor to develop some very interesting technics for investigating the distribution of microbes, pollens and fungus spores in the upper atmosphere and for studying their transport by air currents. Already some important results have been secured in such subjects as the spreading of gypsy moths by their larvae, and the dissemination of a serious fungus disease of wheat.

Many other examples might be added to these which I have purposely selected principally from the field of medicine. Others relate to food technology, industrial hygiene, etc. But let me give one more illustration which illustrates unusually well the possibilities of cooperation of specialists in different fields. I refer to a possible approach to the study of fatigue of automobile drivers.

Professor Horton, an electrical engineer, has developed a very accurate method for measuring the "phase angle" of living tissues. This phase angle expresses the relation between electrical reactance and electrical resistance. In addition to showing a correlation with certain glandular disorders, such as myxedema and Addison's disease, it now appears that the phase angle may be used as a quantitative measure of fatigue. This is not yet certainly established, but if it should be, then the following study of fatigue of automobile drivers would be possible.

The person under investigation will be seated on an automobile seat, with his hands on a steering wheel, and the whole outfit mounted on a shaking table devised by Professor Ruge for study of behavior of small model building structures in the accurately reproduced motion of earthquakes. This reproduced motion is secured by a hydro-electrical apparatus controlled by a beam of light passing through the irregular tooth-like edge of a rotating cam. This tooth-like edge is shaped to reproduce the earthquake motion in the shaking table, and the edge shape is calculated by means of the machine for mechanical solution of differential equations devised by Dean Bush and using earthquake data secured by a special type of seismograph built by Professor Slichter.

By driving any given type of automobile, equipped with such a seismograph, over any given type of road, and operating on this record with the differential analyzer to calculate the required cam shape to make the table shake just as did the automobile on the road, it is obvious that the driver may be given a "synthetic" ride to reproduce the jiggles and bumps of the real ride for any desired duration of time. He can be placed in a compartment like an actual automobile and air-conditioned to reproduce the temperature, stuffiness, carbon monoxide content, etc., of any given driving

conditions By methods devised by Dr De Silva of Harvard, he can even be given the synthetic job of driving in traffic

All this time his phase angle, and hence his fatigue, is being recorded, his reaction time can be tested whenever desired, and any other tests may be made and automatically recorded

If this should be done, we would have brought to bear on the study of fatigue, techniques developed for other purposes by electrical, mechanical and civil engineers, a geologist, a physicist and a psychologist Whether or not this will be done remains to be seen, but it illustrates the possibilities of co-operative effort

Organization Finally, as to organization, I should say that a department of biological engineering should be headed by a biologist, and should include a physicist, an organic chemist, an analytical chemist and an electrical engineer There may be others Then there should be coexistent departments in the scientific and engineering fields whose members can be drawn in for consultation and temporary help, when required, in their respective specialties And there must be a cooperating medical group to handle medical aspects deriving from the program Wherever such an organization can be set up, there I believe that what I have ventured to call "biological engineering" may serve a useful function in promoting the more effective marshalling of our existing knowledge in many fields for the specific objective of advancing our knowledge of biology and its applications to human welfare

In conclusion, I would like to make one comment lest, in my effort to present the case for biological engineering, I may have given the impression that I believe the physical and engineering sciences can step blithely in to lead the biologists to the quick solution of their problems I do not believe this at all, I only believe that there may be an opportunity now for us all to get together more effectively along some such line as I have tried to suggest The main avenue of advance is, and will continue to be, the direct approach through biology, physiology and medicine But these problems are so complex, so vast in scope and human import, that every promising avenue of approach to their solution should be followed And I believe that this avenue of biological engineering shows some real promise of leading in the desired direction

CASE REPORTS

SUBARACHNOID HEMORRHAGE FOLLOWING INJECTION OF EPINEPHRINE*

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EPINEPHRINE is regarded as a harmless drug, the only common contraindications being angina pectoris and hypertension. Its use in the field of allergy is practically universal. Serious complications following its subcutaneous administration are not reported. Hence, we feel that the occurrence of a subarachnoid hemorrhage following the subcutaneous injection of 0.5 cc of epinephrine 1/1000 solution is of sufficient interest to be reported in detail.

SUBARACHNOID HEMORRHAGE

The recognition of subarachnoid hemorrhage as a clinical entity has been greatly simplified since the report of Symonds and Cushing¹ in 1923, dealing with intracranial aneurysm. Previous to this, the reports were largely pathological studies of cases that had not been diagnosed clinically. However, following this contribution, clinical reports² of cases recognized and properly treated during life began to appear in the literature.

Subarachnoid hemorrhage in young adults is by no means an uncommon occurrence. It has been reported as having occurred in some cases at rest, in others during coitus, straining at stool, physical exertion such as weight lifting, emotional upsets such as fright, etc., all of which elevate blood pressure. At times it has occurred during pregnancy, labor and several hours to several days postpartum.³

The underlying factor in this disease, military aneurysm, is most often found in one of the superficial cerebral arteries. In many younger individuals no lesion has been demonstrated at autopsy. Vascular syphilis, arteriosclerosis, infections such as subacute bacterial endocarditis, toxins and chronic alcoholism have been considered important etiological agents. Eppinger⁴ in 1887 was the first to suggest a congenital defect in the vessel wall. Von Hofmann⁵ in 1894 found the favorite site of aneurysm to be at the bifurcations of the cerebral vessels. Fearnside⁶ studied 5432 head examinations of 7924 autopsies and found 44 aneurysms. Forbus⁷ studied the cerebral vessels of a case of subarachnoid hemorrhage. He found that there were multiple aneurysms arising only from vessels of the carotid system and that all were located at the points of bifurcation, with no evidence of inflammation but a definite defect in the muscularis at numerous points of division. No definite muscularis abnormality was demonstrated in the other arteries except at points of bifurcation. The location of the aneurysms corresponded exactly to the location of the muscular defect. This led to the study of embryos in which he found that the

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muscularis of the arteries and that of their branches develop independently. Thus, it was hypothesized that the muscularis may not fuse at the point of bifurcation, leaving a defect. Forbus performed some interesting manometric experiments demonstrating the pressure effects on the points of bifurcation, concluding "Our interpretation of the facts, as we have stated it in this account of multiple miliary aneurysm formation, forces us to the conclusion that multiple aneurysms of the superficial arteries of the brain, as well as those of the arteries of medium size of other organs, are acquired lesions based upon a congenital arterial structural imperfection, a defect in the muscular coat, characteristically located at points of bifurcation." Strauss et al.²¹ found "arteriosclerosis of the cerebral arteries to be the most common pathologic condition responsible for the disorganization of the vessel wall, the aneurysmal formation, the rupture and the hemorrhage into the subarachnoid space, irrespective of the age of the patient."

Briefly, the history obtained in cases of spontaneous⁶ subarachnoid hemorrhage is as follows. There is a sudden onset of intense, severe headache, which may be local or general, causing the patient to "hold the head with pain." It may originate in the back of the neck. A "feeling of something having snapped at the base of the skull" is sometimes described. Nausea and vomiting frequently accompany or follow the pain. At times the patient loses consciousness for a short period following which he may be drowsy and stuporous for varying lengths of time, sometimes going on to coma and death. Due to the blood present in the cerebrospinal fluid, acting as an irritant, there is neck pain and stiffness, Kernig's sign and a mild febrile reaction. Depending on the amount of blood and the location of the clot, there are various localizing signs. The eye grounds may show choked discs and hemorrhages. The pupils may be unequal, dilated or contracted. The pulse may be slow and the blood pressure elevated. Polyuria, glycosuria and albuminuria are encountered at times.

The diagnosis of subarachnoid hemorrhage is usually confirmed by the spinal fluid findings. From's observations⁹ are still considered classical. The spinal fluid pressure is increased and in three successive fractions of fluid the blood is mixed to the same degree. The amount of blood and the color of the fluid vary. The supernatant fluid may be pale orange or brown to golden yellow. No coagulum forms in the fluid. In hemorrhage incident to spinal puncture the amount of blood decreases in the three fractions and coagulates in the fluid, the supernatant fluid is clear and colorless. In subarachnoid hemorrhage the characteristic features are an even admixture of red blood cells, xanthochromia, crenated red blood cells on microscopic examination and absence of coagulum.

In an analysis¹⁰ of 105 cases of subarachnoid hemorrhage Strauss and Tarachow concluded that the prognosis is worse with generalized vascular disease and better where there is no clinically evident hypertension or arteriosclerosis. The older the patient, the worse is the prognosis even without evidence of vascular disease.

In addition to symptomatic and supportive measures drainage of the spinal canal should be done at regular intervals. Authors have varied in their recommendations regarding this procedure but, in general, drainage is usually resorted to until the fluid clears. Pressure readings should be made at each tap.

The course and duration of the illness depend upon the amount of bleeding,

its location and whether there are immediate recurrences. In cases of spontaneous subarachnoid hemorrhage in younger individuals the patient usually improves rapidly during the first week and recovers in three to six weeks.

EPINEPHRINE

Epinephrine causes a rise in blood pressure due to its effect in producing arteriolar constriction. The height of the rise varies with the individual and the method of administration. By the intravenous route, it produces a marked elevation, intramuscularly, the reaction is less, and subcutaneously least of all. "Epinephrine is easily oxidized and when introduced into the circulation it is so rapidly destroyed that an effective concentration in the blood is maintained for only a brief period, hence its evanescent effect" according to Rogoff.¹¹

In experimental animals the response of the pial arterioles to the local application of epinephrine is the same as that of arterioles in other parts of the body.¹² In other animal experiments¹³ it was found that a rise in blood pressure can overcome epinephrine vasoconstriction within the head. These latter experiments also suggest that the drug increases the cerebral circulation. In isolated dogs' heads Bouckaert and Jourdan¹⁴ found that epinephrine produced vasoconstriction when perfused through the arterial system. In a later paper,¹⁴ these workers reported that they had injected strong doses of epinephrine into the general circulation of dogs and had found that the distensive action of the systemic hypertension overcomes the local vasoconstrictive action of the drug. They believed that the musculature of the cerebral arterial walls, excited to constriction by epinephrine, limits the distensive effect of the hypertension. Cachera and Fauvert¹⁵ performed similar experiments on dogs and their results are in agreement with the work of Bouckaert and Jourdan.

Gibbs and his coworkers¹⁶ found in their human subjects "an abrupt and great acceleration of blood flow" following intravenous injections of 0.1 to 0.2 c.c. of 1/1000 solution of epinephrine which was "sufficient to cause a sharp increase in blood pressure and impulse rate." They believed the increase in flow was secondary to the increase in systemic blood pressure. In other cases they used amounts (0.01 to 0.005 c.c.) which did not cause a rise in the blood pressure but in "each instance there was a moderate increase in flow."

It has been stated that no obvious systemic effect is produced in normal individuals after subcutaneous injection of epinephrine, it was believed that absorption from the subcutaneous tissues was so slow that destruction or neutralization kept pace with it.¹⁷ However, in 10 normal males under basal metabolic conditions Blumgart¹⁸ found an increase in the velocity of peripheral blood flow averaging 81 per cent, an increase in the speed of pulmonary circulation averaging 76 per cent, an increase in pulse rate of 12 to 24 beats and an increase in pulse pressure produced by a rise in systolic blood pressure and a fall of the diastolic pressure. He used 0.5 c.c. of 1/1000 solution of epinephrine subcutaneously. Moreover, Jensen¹⁹ found similar blood pressure changes in 13 normal persons injected, using 0.5 to one c.c. of 1/1000 solution of epinephrine subcutaneously. The increase in systolic blood pressure varied from 15 to 85 mm. of mercury, the maximal being reached in 11 to 46 minutes. The immediate response varied from 8 mm. in 22 minutes to 38 mm. in 3½ minutes. In three cases the pressure suddenly increased. Kylin²⁰ used one milligram of epinephrine subcutaneously in normal individuals and found a blood pressure

rise of 15 to 20 mm in one to two minutes. The maximal effect was produced in 5 to 10 minutes. Harman²¹ injected 0.5 cc of 1/1000 solution of epinephrine subcutaneously into women with normal menstrual cycles and found no rise in blood pressure over 8 mm nor in pulse rate over five beats per minute. Myers and King²² injected 10 minims of 1/1000 solution of epinephrine subcutaneously into 10 normal, healthy, white women between the ages of 20 and 30. Four showed no change in systolic blood pressure, five gave an immediate rise of from 8 to 10 mm of mercury, and in one the systolic blood pressure rose 15 mm within eight minutes. In four the diastolic blood pressure fell 10 mm within eight minutes, in six cases there was no essential immediate variation. The diastolic blood pressure in all these cases showed a tendency to a lower level during the period of observation. The pulse pressure varied accordingly, showing an average immediate increase of 10 mm of mercury. The average increase in pulse rate was twelve beats per minute.

CASE REPORT

Mrs M F G, aged 20, a primipara, delivered by low forceps on July 24, 1937. Her puerperium was uneventful until she developed urticaria on August 6, 1937. Except for the occurrence of hives in her mother and brother the family history was inconsequential. The urticarial attack on August 6 was mild, the itching being relieved by calamine lotion and several $\frac{3}{8}$ grain ephedrine sulphate capsules. On the morning of August 7, 1937, these lesions had almost entirely disappeared and there was no itching. That evening about 9 p.m. one of us (B S) was called to see her. At that time she had a severe attack of urticaria with very annoying pruritus. Almost the entire body was red and there were numerous typical urticarial lesions. Dermographia was elicited. An injection of 0.5 cc of 1/1000 solution of epinephrine was given subcutaneously. Within one-half hour the skin was clear and there was no itching. About 45 minutes after the injection she developed a sudden, severe headache which was generalized and increased in intensity during the next two hours. (On later questioning there was no sensation of anything snapping in her head.) About an hour and a half after the injection the patient was given 10 grains of aspirin and three grains of Seconal, which she vomited immediately. She became very restless and apprehensive, complaining bitterly of headache, and vomited again in about 20 minutes. An injection of $\frac{1}{4}$ grain of morphine sulphate was given hypodermically and she slept throughout the night and was drowsy all of the next day (August 8). She vomited several times during the day and was able to retain only a small amount of soft food, awakening at intervals, complaining of severe headache. On August 9 she was stuporous and listless but could be aroused, complained of weakness and severe headache, and soon fell asleep. Her orientation was good. Her temperature was 100.4° F, pulse 48 to 56. The blood pressure was 130 systolic and 80 diastolic. There was marked photophobia. In consultation, one of us (M F) found a very rigid neck, Kernig's sign, slight limitation of external rotation of both eyes, and equal, slightly dilated, reacting pupils. The patient was hospitalized with a provisional diagnosis of meningeal irritation, possibly infectious. On admission the blood and urine were essentially negative except for moderate secondary anemia. Spinal puncture was performed, the findings of which are listed in table 1. A diagnosis of subarachnoid hemorrhage, secondary to epinephrine injection, was made. Dr R G Spurling concurred in the diagnosis. He found no fundal changes. In all, five spinal punctures were done (table 1). The patient improved rapidly and was discharged on August 18, 1937, with slight neck stiffness, moderate photophobia and definite weakness. One month after the onset of this illness she had made a complete recovery.

TABLE I
Record of Spinal Punctures

Date	Pressure in millimeters of spinal fluid	Color and amount of fluid withdrawn	Red blood cell count	White blood cell count	Differential count	Remarks
8/9	190	Very bloody Bright red Very cloudy 25 c c	250,000	222	All poly's	Supernatant fluid slightly xanthochromic B P 130/80
8/10	130	Bloody Bright red (less than above) Cloudy 20 c c	20,500	0-1	All poly's	Increased xanthochromia B P 114/64
8/11	30	Light orange to amber Cloudy 15 c c	30,000	65	91% poly's 9% lymph's	Xanthochromic B P 110/60
8/13	110	Light amber Slightly cloudy 8 c c	10,000	60	74% poly's 25% lymph's 1% mono	Xanthochromic B P 120/80
8/16	110	Light amber Very light cloud 4 c c	35-40	8-10	96% lymph's 4% poly's	Xanthochromic

COMMENT

This case has many interesting features. Assuming that there actually existed a congenital aneurysm, how did it withstand the stress and strain of labor only two weeks previously? It is true that the second stage was considerably shortened by low forceps delivery yet at some time during labor there must have been some strain. It is possible that this exertion weakened the aneurysmal wall sufficiently so that the rise in blood pressure and the increase in cerebral circulation volume and velocity, after the injection of epinephrine, were able to cause its rupture. It is probable that this individual is unusually responsive to epinephrine and had a sudden, sharp rise in systemic blood pressure and marked distention of the cerebral arterial system. The possibility that some of the material injected entered the venous circulation cannot be overlooked.

A search of the literature has revealed no case of subarachnoid hemorrhage under similar circumstances. Symonds²³ writes "I have not met with or heard of a similar case." We feel that the unusual circumstances associated with this accident warrant this report.

SUMMARY

Herein is reported an instance of subarachnoid hemorrhage in a young woman two weeks postpartum following an injection of 0.5 c c of 1/1000 solu-

tion of epinephrine subcutaneously The modus operandi is suggested The patient recovered

BIBLIOGRAPHY

- 1 SYMONDS, C P, and CUSHING, H Contributions to the clinical study of intracranial aneurysms, *Guy's Hosp Rep*, April, 1923
- 2 a SYMONDS, C P Spontaneous subarachnoid hemorrhage, *Quart Jr Med*, 1924, xviii, 93
b GOLDFLAM, S Beitrage zur Atiologie und Symptomatologie der spontanen subarachnoidalen Blutungen, *Deutsch Ztschr f Nerven*, 1923, lxxvi, 158
c McIVER, J, and WILSON, G Spontaneous subarachnoid hemorrhage, *Jr Am Med Assoc*, 1923, xciii, 89
d BARKER, L F Spontaneous subarachnoid hemorrhage, *ANN INT MED*, 1936, x, 98
e See references 1, 3a, 3b, 3d
f SAVITSKY, N Diseases of the meninges, *Nelson Loose Leaf Medicine*, Volume VI, Chap XXV, p 5491
g TAYLOR, A B, and WHITFIELD, A G W Subarachnoid hemorrhage, *Quart Jr Med*, 1936, v, 641
h SCHMIDT, M Intracranial aneurysms, *Brain*, 1930, liii, 489
i STRAUSS, I, GLOBUS, J H, and GINSBURG, S W Spontaneous subarachnoid hemorrhage, *Arch Neur and Psych*, 1932, lxxvii, 1080
- 3 a SCHWENKENBURG, A J Spontaneous subarachnoid hemorrhage, *Texas St Med Jr*, 1933, xxviii, 814
b RUSSELL, C K Spontaneous subarachnoid hemorrhage, *Canad Med Assoc Jr*, 1933, xxviii, 133
c STROINK Subarachnoid hemorrhages in connection with pregnancy, *Nederl tijdschr v verlosk en gynaec*, 1936, xxxix, 240
d SMITH, W A Spontaneous subarachnoid hemorrhage, *South Med J*, 1930, xxiii, 494
- 4 EPPINGER as quoted by Fearnside⁶
- 5 VON HOFMANN as quoted by Fearnside⁶
- 6 FEARNSIDES, E G Intracranial aneurysms, *Brain*, 1916, xxxix, 224
- 7 FORBUS, W D On the origin of miliary aneurysms of the superficial cerebral arteries, *Bull Johns Hopkins Hosp*, 1930, xlvii, 239
- 8 Spontaneous is taken to mean non-traumatic Symonds^{2a}
- 9 FROIN, G These de Paris, No 113, 1904 As quoted by Symonds^{2a}
- 10 STRAUSS, I, and TARACHOW, S Prognostic factors in spontaneous subarachnoid hemorrhage, *Arch Neur and Psych*, 1937, xxxviii, 239
- 11 ROGOFF, J M The adrenal medulla, glandular physiology and therapy, *Am Med Assoc*, 1935, Chap XIX, p 279
- 12 FORBES, FINLAY and NELSON as quoted by Gibbs et al¹⁶
- 13 FINESINGER and PUTNAM as quoted by Gibbs et al¹⁶
- 14 BOUCKAERT, J J, and JOURDAN, F Effects of adrenalin and excitation of cervical sympathetics on the isolated intracranial circulation, *Compt rend Soc de biol*, 1935, cxx, 84
Idem *ibid*, 1935, cxx, 255
- 15 CACHERA, R, and FAUVERT, R Effects of adrenalin on the cerebral circulation, *Compt rend Soc de biol*, 1936, cxxii, 365
- 16 GIBBS, F A, GIBBS, E L, and LENNOX, W G The cerebral blood flow in man as influenced by adrenalin, caffeine, amyl nitrite, and histamine, *Am Heart Jr*, 1935, x, 916
- 17 SOLIS-COHEN, S, and GITHENS, T S *Pharmacotherapeutics*, 1928, D Appleton & Co, New York, p 1462

- 18 BLUMGART, H L The circulatory response to epinephrine, Libman Anniversary Volumes, The International Press, New York, Vol I, p 215
- 19 JENSEN, J The adrenalin test in hypertension, Am Heart Jr, 1930, v, 763
- 20 KYLIN, E Ztschr f klin Med, 1926, ciii, 233, As quoted by Myers and King ²²
- 21 HARMAN, J H Brit Med Jr, 1927, ii, 14, As quoted by Myers and King ²²
- 22 MYERS, W K, and KING, J T Observations on the menopause, Bull Johns Hopkins Hosp, 1930, xlvii, 22
- 23 Personal communication to the authors

HEMOLYTIC STREPTOCOCCIC ANGINA WITH AGRANULOCYTOSIS TREATED WITH PRONTOSIL AND SULPHANILAMIDE *

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THE fundamental discovery by Domagk ¹⁻⁴ of the protective action of certain sulphonamide derivatives of the azo dyes in experimental hemolytic streptococcic infection, and the supplementary demonstration by Tréfouel, Tréfouel, Nitti, and Bovet ⁵ of the similar action of para-aminobenzenesulphonamide, have received abundant confirmation ⁶⁻¹³ From the date of Domagk's original publication ¹ an ever increasing volume of clinical reports has been appearing in the current medical periodicals concerning the favorable influence of these chemotherapeutic agents in the treatment of the various types of hemolytic streptococcic infection This literature has contained scattered references to the therapeutic results obtained in the treatment of acute pharyngitis, tonsillitis, and peritonsillar abscess ^{14-19, 12, 20} Although a brief report on a similar case by Schur and Singer ²¹ has already appeared, the present report is the earliest detailed record of the clinical course and laboratory findings in the treatment with Prontosil and sulphanilamide of a fulminant necrosing pharyngitis accompanied by a complete agranulocytosis

CASE REPORT

On September 2, 1936, A McM, a white male, 52 years of age, suddenly developed sharp lightning-like pains with deep boring sensations in the shafts of the right and left femurs and along the crest of the left tibia The pains, which were very severe and exhausting, did not appear to follow the course of either the femoral or sciatic nerve distribution They recurred at frequent intervals over a period of several days

On September 3 an indefinite soreness of the throat, with chilliness, a rapidly rising temperature, headache, and generalized body aches, confined the patient to bed

On September 4 the patient was first seen by the physician The muscle, joint, and bone aches, which were causing the most acute distress, were still the chief complaint Four or five years previously the patient had been affected with some bone disease in the region of the right hip, for which an operation had been performed and a cast applied But no tenderness was to be elicited on palpation or pressure over any of the affected bones The throat soreness had increased and pain on swallowing had developed The throat was very much reddened and inflamed, but no spots, patches, or areas of pseudo-membrane formation were visible The tonsils had been

* Presented before the Staff Meeting of the Bay Ridge Hospital, Brooklyn, New York, May 4, 1937

removed years before but some tissue fragments remained. The patient had suffered from several attacks of throat infection of ordinary severity during the preceding three years. The temperature was 101°.

The clinical picture was that of the usual septic sore throat. Treatment was instituted on this basis. The affected areas of the throat were painted with a 3 per cent solution of iodine in glycerin, an injection of a non-specific protein antigen was administered subcutaneously, and a mixture containing salicylates and gelsemium prescribed for internal medication, perborate of soda as a mouthwash and gargle, and cold compresses to be applied externally, were recommended. Against advice, but for reasons of economy, the physician was requested to return only on call.

Four days later, on September 8, the physician was called again. The pharynx, tonsillar areas, and uvula now showed one extended mass of grayish-black necrotic membrane. The patient was confused and drowsy. The bone pains had ceased and the body aches were less, but the headache, which was somewhat localized at the back of the neck, was worse. The breath was foul. The temperature was 107° F by mouth. The injection of 10,000 units of diphtheria antitoxin, which was given immediately on the impression that a septic diphtheria had developed, was without effect.

On September 9 the throat smears and cultures, which had been sent to the laboratory, were reported to show a preponderance of streptococci of the hemolytic strain, as well as many other organisms, but no Klebs-Löffler bacilli, or fusiform bacilli and spirochetes. The white blood cell count and differential was reported to show only 1200 cells consisting entirely of lymphocytes with a complete absence of polymorphonuclears.

The final diagnosis, which was first made at this time, was therefore hemolytic streptococcic angina with a complicating agranulocytosis. There was no recent history of having taken any amidopyrine or related drug containing the pyrazolon nucleus. The prognosis was regarded as very grave.

By this time the patient was obviously critically ill. The skin was hot and flushed. The breath was very foul. Deglutition was practically impossible as fluids returned through the mouth and nose. Moderate swelling of the cervical nodes had taken place. The patient was stuporous, and the deep reflexes were greatly diminished. Yet examination of the heart and lungs was negative. The kidneys were functioning, the urine contained no albumin, sugar, casts, or pus.

Under these conditions the fight against this fulminating hemolytic streptococcic angina and the potentially fatal agranulocytosis was begun. Treatment was instituted under trained nurses in the home. After two days the patient was removed to the Methodist Episcopal Hospital in Brooklyn, New York. The statistics of agranulocytosis from all causes at this hospital, from 1928 to 1936, show in a series of 13 cases, 10 deaths and 3 recoveries.

Specific treatment was carried out on two lines: first, for the control of the hemolytic streptococcic infection, Prontosil and sulphanimide, second, for the agranulocytosis, pentnucleotide and Liver Extract.

Prontosil solution was injected intramuscularly in 5 c.c. doses at four hour intervals five times in 24 hours. Sulphanilamide (Prontylin) tablets were crushed and given in watery suspension by means of a nasal tube in doses of 15 grains four times in every 24 hours.

Pentnucleotide was injected intramuscularly in 10 c.c. doses daily. Concentrated parenteral solutions of liver extract were injected intramuscularly in 3 c.c. doses twice on every other day.

Local treatment consisted of throat irrigations at two or three hour intervals with hot solutions of one-half per cent permanganate of potash alternating with weak solutions of perborate of soda or bicarbonate of soda.

Supportive treatment included a high fluid intake and frequent liquid feedings given by means of a Levine nasal tube, solutions of glucose intravenously, and 1/60 of

a grain of strychnin arsenate and 3 minims of a 1 1000 solution of epinephrine chloride subcutaneously, twice or thrice daily Intestinal elimination was aided by means of enemata

In response to these measures a striking therapeutic result was obtained in combating the destructive pharyngeal infection and the total suppression of the granulocytes This therapeutic result consisted in the subsidence of the toxemia, the healing of the throat lesion, and the concomitant regeneration of the polymorphonuclears The remarkable reaction of the patient to the treatment was soon evident

The maximum and minimum temperatures were appreciably lower on each succeeding day of treatment, and after the fourth day the temperature dropped sharply to normal (table 1, figure 1) The mental confusion and stupor lessened The general condition of the patient improved

TABLE I

Days from onset	Temperature		Leuko-cytes	Lymphocytes				Granulocytes										Mono-cytes	
	Maxi-mum	Mini-mum		Large		Small		Perny elocytes		Mycytes		Metamye-lo-cytes		Neutro-philcs		Baso-philcs			
				per cent	num ber	per cent	num ber	per cent	num ber	per cent	num ber	per cent	num ber	per cent	num ber	per cent	num ber		
3	101																		
7	107		1,200	32	374	68	826												
8	104.3	101.8																	
9	104.8	102																	
10	103.6	103	2 100	24	504	76	1 596												
11	103.6	99.8	1 900	26	494	71	1,349							3	57				
12	102.6	98.6																	
13	100.6	98.6	4 500	15	675	53	2,380							31	1,395			1	45
14	100.6	100.2	9 100	9	819	46	4 186	3	273	6	546	7	637	29	2 639				
15	100.6	99	11 900	13	1 547	27	3 213	2	238	4	476	23	2,737	31	3,689				
16	100.6	99	16 000	8	1,280	17	2,720	2	320	5	800	33	5,280	35	5,600				
17	100.4	99.2	16 000	11	1 760	23	3 360			2	320	31	4,960	35	5 600				
18	100.4	99	15 628	7	1,152	9	1,480			1	165	36	5,022	42	6 931			5	822
19	100	99.4																	
20	99.6	98.8	17 550	4	702	6	1,053							90	15,795				
21	99	98	12 700	11	1 397	18	2 266							71	9 017				
22	98.6	98	9 850	9	887	15	1,477							76	7,486				
23	98.8	98	11,600	8	928	14	1,624							76	9,048	2	232		
24	98.6	98.6																	
25	98.8	98.2																	
26	98.6	98																	
45			6 400	4	256	49	3 136							47	3 008				

By the seventh day a decided change was evident in the condition of the throat The offensive odor had disappeared The thickness and tenacity of the membrane began to decrease, and a gradual exfoliation resulted

From the time of the highest temperature when the blood was first examined the number of both the large and the small lymphocytes per cubic millimeter showed a gradually increasing upward trend Granulocytes first reappeared in the blood between the second and the third day of treatment, or during the interval when the fever was slowly receding Almost from the time of their reappearance the polymorphonuclear neutrophils showed a rapidly increasing upward trend, but by the time when the temperature had reached normal were present in less than one-third their normal number (table 1, figure 1)

On September 14 the temperature rose abruptly to 100.6° where it remained practically constant for a day and a half From then on it fluctuated consistently for several days between about 99° in the morning and 100.5° in the afternoon

Duplicate blood cultures in broth were made at the onset of this secondary rise in temperature One was negative The other showed a slight delayed growth of hemolytic streptococci Nevertheless the existence of a bacteremia was questioned

Inasmuch as these streptococci proved to be of a short chain strain, unlike that isolated from the throat, they were felt to have been a contaminant

With the secondary rise in temperature a slight increase in the number of large lymphocytes and a marked increase of small lymphocytes occurred. A brief spurt of premyelocytes, a prolonged wave of myelocytes, an increasing flood of metamyelocytes and polymorphonuclear neutrophils and a final surge of monocytes also entered the blood. As a result, the leukopenia which remained after recovery from the agranulocytosis was replaced by a marked leukocytosis (table 1, figure 1)

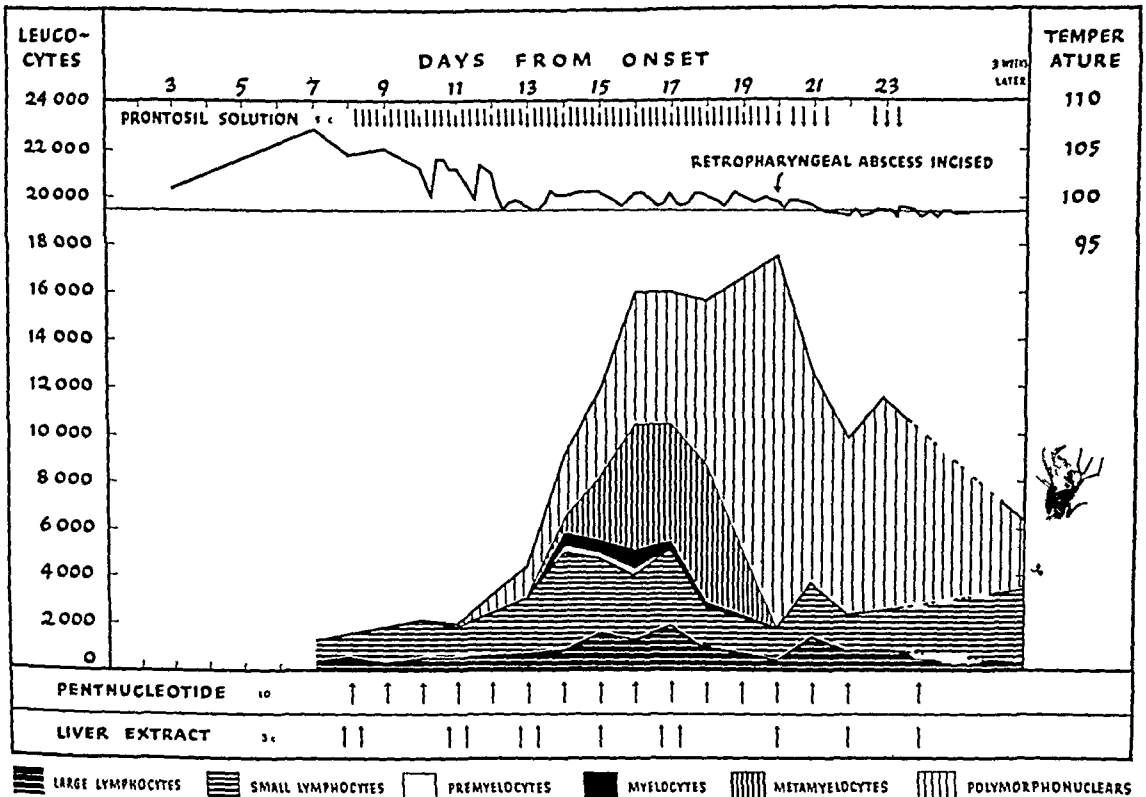


Fig 1 Hemolytic streptococcic angina with agranulocytosis temperature chart, blood picture, and medication

During the development of this leukocytosis it was observed that most of the leukocytes showed pronounced toxic degenerative changes. On this account it seemed advisable, in view of the sustained fever which, at the time, could not be satisfactorily explained, to resort to a blood transfusion. On September 16 a transfusion of 300 c.c. of type IV blood was accordingly given.

On September 18 a tendency toward urinary retention developed which required the use of the catheter for several days.

This low grade fever proved to be the result of a large abscess which had formed in the retropharyngeal space. On September 21 the retropharyngeal abscess was opened and freely drained of a large amount of greenish-yellow pus. The next day the power to swallow returned in sufficient degree to permit of the discontinuance of the nasal tube. Following the drainage of the abscess the temperature rapidly approached normal and remained so for the remainder of the convalescent period as the patient went on to make a complete recovery.

The polymorphonuclear leukocytosis continued to increase up to the time when the retropharyngeal abscess was incised. The excess of neutrophils in the blood then receded, rapidly at first, but more gradually later.

After September 21 the injections of Prontosil solution were reduced, first to three a day, then to three on every other day, of Pentnucleotide to one every other day, and of liver extract to one every second or third day

On September 28 all medication was discontinued, and the patient was discharged from the hospital

During the period of the absolute agranulocytosis the red cell count was 4,800,000, the hemoglobin 66 per cent, and the color index 0.69. The blood platelets maintained a count of between 150,000 and 200,000 throughout the illness. After the final subsidence of the fever the red cell count at 4,200,000 and the hemoglobin at 65 per cent were only slightly below normal levels. Repression of blood cell formation in the bone marrow was evidently confined entirely to the granulocytes.

Subsequent to recovery a complete blood examination showed a white cell count of 6,400 leukocytes divided about equally between 3,000 granulocytes and 3,400 lymphocytes, a red cell count of 3,900,000 (table 1, figure 1), hemoglobin 73 per cent, and a color index of 0.93. The fact that there was a relatively high number of lymphocytes and a relatively low number of neutrophils in the blood following recovery might suggest the presence of some degree of deficiency in the formation of the granulocytes.

In this case Prontosil and sulphanilamide evidently exerted a definite and specific action against the hemolytic streptococcal angina with a resulting suppression and elimination of the toxic focus that was causing the arrest of the maturation of the myeloblastic cells in the bone marrow. As soon as the production by the hemolytic streptococci of the toxins, which had a selected action against the leukocytes of the granulocytic series, was checked, time was permitted for the regeneration of the polymorphonuclears and the repair of the local damage sustained by the pharyngeal structures. The restoration of the maturation of the myeloblastic cells was, in all probability, abetted through their stimulation by Pentnucleotide and liver extract.

REFERENCES

- 1 DOMAGK, G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, *Deutsch med Wchnschr*, 1935, *lx*, 25-253
- 2 HORIEN, H. The chemotherapy of infectious diseases caused by protozoa and bacteria, *Proc Roy Soc Med*, 1935, *xxix*, 313-324
- 3 DOMAGK, G. Chemotherapie der bakteriellen Infektionen, *Angew Chem*, 1935, *xlvi*, 657-667
- 4 DOMAGK, G. Chemotherapie der Streptokokken-Infektionen, *Klin Wchnschr*, 1936, *xv*, 1585-1590
- 5 TREFOUEL, J., TREFOUEL, J. (Mme), NITTI, F., and BOVER, D. Activite du p-aminophenylsulfamide sur les infections streptococciques experimentales de la souris et du lapin, *Compt rend Soc biol*, 1935, *cx*, 756-758
- 6 LEVADITI, C., and VAISMAN, A. Action curative et preventive du chlorhydrate de 4'-sulfamido-2, 4-diaminoazobenzene et de quelques derives similaires dans la streptococcie experimentale, *Compt rend Acad d sci*, 1935, *cc*, 1694-1696, *Compt rend Soc de biol*, 1935, *cxix*, 949-951, *Presse med*, 1935, *xlvi*, 2097-2102
- 7 NITTI, F., and BOVER, D. Action du 4-sulfonamide-2,4-diaminobenzol (Prontosil) sur des infections streptococciques de la souris provoques par des streptocoques d'origine humaine, *Compt rend Soc de biol*, 1935, *cxix*, 1277-1280
- 8 GOISSEDET, P., DESPOIS, R., GAILLIOT, P., and MAYER, R. De l'action du radical sulfamide SO_2NH_2 sur l'infection streptococcique experimentale de la souris, *Compt rend Soc de biol*, 1936, *cxli*, 1082-1084

- 9 COLEBROOK, L, and KENNY, M Treatment of human puerperal infections, and of experimental infections in mice, with prontosil, *Lancet*, 1936, ccv, 1279-1286
- 10 BUTTLE, G A H, GRAY, W H, and STEPHENSON, D Protection of mice against streptococcal and other infections by p-aminobenzenesulphonamide and related substances, *Lancet*, 1936, ccv, 1286-1290
- 11 COLEBROOK, L, BUTTLE, G A H, and O'MEARA, R A Q The mode of action of p-aminobenzenesulphonamide and prontosil in hemolytic streptococcal infections, *Lancet*, 1936, ccv, 1323-1326
- 12 LONG, P H, and BLISS, E A Para-aminobenzenesulfonamide and its derivatives experimental and clinical observations on their use in the treatment of beta hemolytic streptococcal infections, *Jr Am Med Assoc*, 1937, cviii, 32-37, *Arch Surg*, 1937, lxxiv, 351-358
- 13 LONG, P H, and BLISS, E A The use of para-aminobenzenesulphonamide (sulphanilamide) or its derivatives in the treatment of infections due to beta hemolytic streptococci, pneumococci, and meningococci, *South Med Jr*, 1937, xxx, 479-487
- 14 KLEE, P, and ROMER, H Prontosil bei Streptokokkenkrankungen, *Deutsche med Wchnschr*, 1935, lxi, 253-255
- 15 SCHRANZ, H Zur Sepsisbehandlung mit Prontosil, *Munchen med Wchnschr*, 1935, lxxxii, 419-420
- 16 RECKNAGEL, K Erfahrungen mit Prontosil, *Munchen med Wchnschr*, 1935, lxxxii, 704-706
- 17 HOFMANN, E Erfahrungen mit Prontosil bei septischen Erkrankungen, *Fortschr Ther*, 1935, xi, 762
- 18 SCHEURER, O Unsere Erfahrungen mit Prontosil, *Med Klinik*, 1936, lxxxiii, 739-742
- 19 DAVIS, E D D Acute streptococcal infections of the throat, *Lancet*, 1936, 375-376
- 20 ROBERTS, S E Will prontosil master streptococcus? *Kansas City Med Jr*, 1937, xiii, 4-7
- 21 SCHUR, M, and SINGER, K Ein Fall von geheilter septischer Agranulocytose, *Wien med Wchnschr*, 1937, lxxxvii, 186

RARE SEQUELAE OF PNEUMONIA, SUBCUTANEOUS, INTRAMUSCULAR AND RENAL ABSCESES CAUSED BY TYPE XIV PNEUMOCOCCUS*

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THE pneumococcus is seldom regarded as the cause of either skin or kidney lesions yet a few reports of such occurrences have been published. A number of observers describe the appearance of non-specific skin eruptions during pneumonia,¹ but others record the actual isolation of pneumococci from the lesions.² Mann and Gerboth² recovered pneumococci from a nodular eruption on the legs. Wakefield's patient with type II pneumococcal pneumonia developed intramuscular abscesses in the deltoid region and on the thigh. Schmidt-LaBaume and Otto noted vesicular lesions on the skin and mucous membranes from which pneumococci were isolated. Subcutaneous abscesses were noted in two of Preble's³ patients. Finland³ recorded 10 cases of subcutaneous abscesses caused by pneumococci but not associated with pneumonia, three were caused by type III pneumococci, two each by types II and XI, and one each by types VII, VIII, and XIV.

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From the Department of Medicine, Jefferson Hospital

Urinary tract infection associated with or caused by pneumococci appeared to be equally uncommon until the recent report of Moor and Brown⁴ who found pneumococci of type XIV in the urine of an amazingly high proportion of patients. Practically none of the previous observers have even recorded the pneumococcus as the causative organism of urinary tract infections, yet in many cases the bacteria found have merely been entered as "cocci" in their statistical tables. Complete identification has seldom been made. Actual renal pneumococcus infection during or after pneumonia is very uncommon. Fahr⁵ observed two instances with multiple renal abscesses and Reimann⁶ reported a case with multiple kidney abscesses caused by type III pneumococci.

In the following case multiple subcutaneous, intramuscular, and renal abscesses were observed following type XIV pneumococcus pneumonia.

CASE REPORT

History A colored man, aged 27, was admitted to the medical service of Dr H A Reimann, four days after the onset of type XIV pneumococcus pneumonia which followed a cold. The right lower lobe was consolidated and a friction rub was present. Vomiting and diarrhea occurred early in the course and the patient appeared to be very ill. A blood culture was sterile. The blood Wassermann reaction was positive. The temperature after admission to the hospital reached 40° C (104° F) during the remainder of the first week of illness, then gradually declined and became normal on the fourteenth day. On the fifteenth day the temperature rose to 38.4° C (101° F) and an abscess was noted over the sacrum which was incised and drained two days later. The pus contained a pure culture of type XIV pneumococci. The temperature thereafter fluctuated irregularly between normal and 39.1° C (102° F) for the rest of the observation period. Another abscess, 2.5 cm in diameter also containing type XIV pneumococci in pure culture appeared two weeks later in the anterior abdominal wall. At the same time pain and tenderness were noted in the left interscapular region. A few days later a swollen, tender area 8 cm by 4 cm developed. Pus was aspirated. The abscess burrowed and spread under the muscle layers and skin to the right interscapular and cervical region. Upon deep incision and drainage 240 cc of thick pus were obtained from which type XIV pneumococci were isolated. The wound healed after a week.

The patient did not recover satisfactorily, the temperature reached fever levels daily and pyuria was noted on the forty-eighth day of illness. Type XIV pneumococci were recovered from the urine on several occasions but two blood cultures were negative. Examination of the abdomen revealed a large tender mass on the left side and a vaguely palpable mass on the right. A diagnosis of pneumococcus pyelonephritis was made. The leukocytes hovered between 11,000 and 20,000 per cu mm. The blood urea nitrogen was 14 mg per 100 cc. The non-protein nitrogen rose progressively from normal to high levels and measured 111 mg shortly before death. The urea clearance test a month after pyuria appeared was 44 per cent of normal, and after two months, 33 per cent of normal. Because of the evidence of increasing retention, left nephrostomy was performed by Dr T Fetter on the eighty-second day. Congenital polycystic kidneys with multiple abscesses were found. Drainage was maintained, but the patient became progressively worse and died four months after the onset of the pneumonia.

Necropsy performed by Dr B L Crawford revealed that the lung lesion had healed. Chief interest focused on the enormous kidneys which weighed approximately 1700 gm each and measured about 26 by 11 by 8 cm. The organs were composed of multiple cysts filled with pus and blood and no normal kidney structure was seen grossly. The chief pathologic diagnosis was polycystic kidneys, and suppurative nephritis.

SUMMARY

A case of type XIV pneumococcus pneumonia was observed in which multiple subcutaneous and intramuscular abscesses, and renal abscesses superimposed on polycystic kidneys, occurred as sequelae. Type XIV pneumococcus is known to be especially invasive and the renal infection was assumed to be the result of infection of congenitally abnormal organs which seem to be especially vulnerable. There is also a probability that syphilis played a rôle in reducing the patient's resistance to pneumococcus invasion. It is of further interest to speculate on the peculiar affinity of type XIV pneumococci for the urinary tract as suggested by the studies of Moor and Brown.

BIBLIOGRAPHY

- 1 HIRSCH, H. Petechiales Exanthem bei Pneumokokkenkrankung, *Med. Klin.*, 1920, vii, 181-184.
- JACOB, L. Beiträge zu Kenntnis der Pneumomykosen, *Jahrb. Hamburgischen Staatskrankenanstalten*, 1909, xiv, 47-87.
- 2 MANN, S. Über fibrinöse Schleimhautentzündung durch Pneumokokkeninfektion, *München med. Wchnschr.*, 1909, ii, 72-74.
- GERBOTH, J. Pneumokokken als Erreger von Hautgangran, *Dissert. Leipzig*, 1911.
- WAKEFIELD, E. G. Intramuscular abscesses complicating pneumonia, *Ann. Clin. Med.*, 1927, v, 804-807.
- SCHMIDT-LABAUME, F., and OTTO, C. Zur Klinik, Histologie und Pathogenese der Pneumokokkenexantheme, *Arch. f. Dermat. u. Syph.*, 1933, clxix, 431-435.
- WINDHOLZ, F. Untersuchungen über metastatische Pneumokokkendermatosen, *Beitr. z. path. Anat. u. z. allg. Path.*, 1924-1925, lxxiii, 432-438.
- 3 PREBLE, cited by HOWARD, C. P. The diagnosis and treatment of pneumonia, *Oxford Univ. Press*, 1936.
- FINLAND, M. The significance of specific pneumococcus types in disease, *Ann. Int. Med.*, 1937, x, 1531-1544.
- 4 MOOR, H. D., and BROWN, I. L. The occurrence of *Diplococcus pneumoniae* in the urinary tract, *Jr. Bact.*, 1937, xxxiii, 73-74, *Jr. Am. Med. Assoc.*, 1937, cviii, 1594-1596.
- 5 FAHR, T. Pathologische Anatomie des Morbus Brighti, *Handb. d. spez. path. Anat. u. Histol.* Henke-Lubarsch, vi, 156-172.
- 6 REIMANN, H. A. Infections of the kidney. The kidney in health and disease, Chapter 20, 1935, Berglund and Medes, Lea and Febiger.

EDITORIAL

SHOULD LOBAR PNEUMONIA BE TREATED IN A HOSPITAL?

No question arising frequently in the daily practice of medicine involves more factors. It may be of interest to consider some of them in the light of present day methods in the treatment of the disease.

The facilities which are available in the home are naturally a first consideration. In impoverished patients the lack of such essentials as an adequate room, heat, light and equipment may at once settle the question in favor of the hospital, provided a well equipped hospital is within reach. Where the home can provide a suitable room and minimum equipment one must consider further matters.

What can be done in the home, for instance, to provide 24 hour nursing service? If graduate nurses are to be available this question is settled, but if they cannot, then probably special nurses could not be provided in the hospital for the same economic reasons.

Most private pavilions do not provide sufficient floor nurses to give adequate care and supervision to a pneumonia patient secluded in a private room. The patient usually fares better in these respects on the wards. The better type of practical nurses, or even intelligent strong women relatives will furnish closer supervision of the patient and better minor nursing care in the home than can be furnished to the patient on "floor care" by either ward or private pavilion. On the other hand in such important matters as hypodermic medication, proper recording of pulse and temperature and assisting the physician in giving serum, oxygen, etc., and reporting on the patient's condition, the partially trained nurse is often inadequate.

When matters are closely balanced between home and hospital as to nursing care, other considerations will decide the issue. The first of these, of course, is the matter of typing, cultures and serum administration. The hospital has strong practical advantages in all these respects. In fact in many instances it may be said that adequate use of these important aids to diagnosis, prognosis and efficient therapy is impossible in the home. On the other hand, given a home not too far from a modern laboratory and an energetic physician trained in the technic of serum administration, it becomes quite possible to give the patient in the home every advantage in this respect afforded by a hospital.

The use of oxygen therapy is likewise quite feasible in the home if the home is within range of one of the commercial houses which rent and service oxygen tents. Its efficient use, however, depends largely upon the quality of the nursing care available and upon the experience of the doctor in the supervision of this form of treatment. Moreover the expense of such oxygen therapy is often prohibitively great when provided in the home, whereas hospitals are apt to be more lenient in this respect.

A very important further point is the closeness of the physician's office to the home of the patient and the amount of time he can devote to the care of the patient. The task of caring for a case of pneumonia outside the hospital in a manner comparable to the routine of a good institution is not one to be undertaken by a man already heavily burdened with other very ill patients. Unless time can be given to the details of serum administration, for instance, its hazards will be notably increased. In considering this problem, however, the physician may well look realistically at the character of the professional care which can be furnished by the best available hospital. There may be no real benefit gained in this respect by placing the patient in a hospital which has no intern staff or in which the dependability of the house staff leaves much to be desired.

There are complications of pneumonia which may greatly add to the difficulties of home treatment: retention of urine, persistent vomiting, severe abdominal distention, certain types of delirium. There are others which may demand surgical intervention such as empyema, purulent pericarditis, or pneumococcic arthritis.

The problem of transportation to the hospital will often be an important one. Distance, roads, weather and the type of ambulance available must be given thought. In general, pneumonia cases stand transportation for reasonable distances in a good ambulance quite well during the first two or three days of their illness, but in the later stages of the disease such a move is a real handicap and may prove an immediate hazard.

The economic side should be considered by the physician only in this far. He owes it to the family to estimate for them, when asked, what the best treatment will cost in either place. It is their problem to determine what funds they can raise, the physician's to see that such funds are spent to the best advantage of the patient.

It is certain that the part of wisdom for the physician is to consider these and other individual factors carefully before coming to his decision. The decision should, however, be reached early and adhered to. There should be no moving of the patient late in the disease and because he is doing badly. The battle should be fought out in the home or in the hospital as seems best in the individual instance.

REVIEWS

Injection Treatment of Hernia By CARL O RICE, M D, F A C S, Instructor in Surgery, University of Minnesota School of Medicine, with the assistance and cooperation of HAMLIN MARTSON, M D 266 pages, 14.5 × 23 cm F A Davis Company, Philadelphia 1937 Price, \$4.50

Velpeau, in 1835, observed the accidental curing of a hernia, following the injection of a hydrocele with an iodine solution. He is given credit as the first physician to treat hernia by the injection method. Jaynes, in 1832, injected essential oils to cure hernia, and probably deserves priority. Dr Ignatz Mayer, of Detroit, is credited with modernizing the injection treatment of hernia. He reported 2100 cases, from 1927 to 1932, with 98 per cent successful results.

The authors feel that ready acceptance of this method has been impeded, because of confusion with the injection of paraffin, and because at times charlatans and unlicensed practitioners have attempted it. The clinical aspects of the book are based on experience as obtained in the Hernia Clinic of the Minneapolis General Hospital, and in private practice. A detailed classification of hernias, anatomical relationships, and etiological factors are discussed. The importance of differential diagnosis is emphasized. A suitably fitting truss is considered mandatory for the cure of a hernia by this method. Suggestions for the selection and fitting of a truss are given. The comparative merits of various sclerosing solutions are described, along with a detailed technic of injection. Indications, contra-indications, complications and sequelae are discussed. The literature is reviewed and a comparison is made with the surgical treatment of hernia. A chapter is devoted to the histopathology of the injection treatment, in which the response of tissue to sclerosing solutions is demonstrated.

The final chapter is devoted to the medico-legal aspects of hernia, with a review of the various state laws.

It is a valuable contribution for those interested in the problem of the treatment of hernia.

G H Y

Principles and Practice of Medicine By SIR WILLIAM OSLER, M D, F R C P, F R S, revised by HENRY A CHRISTIAN, M D, LL D, S D, F R C P Thirteenth Edition 1424 pages, 17 × 25 cm D Appleton-Century Company, New York and London 1938 Price, \$9.00

The thirteenth edition of this time-honored textbook of medicine has been revised by Dr Henry A Christian who in the preface assumes "responsibility for all changes and additions not credited by name to some other." In so doing Dr Christian has given the book a conservative and sound uniformity of style which is lacking in some other texts. More than 200 pages have been added. Typhoid fever has been displaced from its leading position in favor of the more common pneumococcic infections.

The sections on deficiency diseases, blood forming organs and diseases of the circulatory system have been rearranged and brought up to date. Cinchophen has been included as a cause of toxic jaundice, and the discussion of arthritis has been lengthened and improved. New sections on lipid metabolism and on von Gierke's disease have been added.

There is a good discussion on protamine zinc insulin, but no mention is made of those cases in which, for various reasons, it must be discontinued. Lobectomy is recommended in the treatment of bronchiectasis. In sharp contrast to this vigorous

therapy, the ridiculously small dose of 2 to 4 c c of paraldehyde is advised in the treatment of delirium tremens. The precedent of former editors in not mentioning the psychoses has been followed. To the reviewer, this seems a mistake.

Dr Christian is to be congratulated on the many improvements which he has made. It may be hoped that his assumption of the editorship of this text will restore much of its lost popularity. The book is recommended for use by both student and practitioner.

L P G

Pathology of the Central Nervous System By CYRIL B. COURVILLE, M.D. 344 pages, 17 × 25.5 cm. Pacific Press Publishing Association, Mountain View, California. 1937. Price, \$5.75.

This book was written for the use of students and the general reader. It is based on a study of some 15,000 autopsies done in a general hospital, and therefore represents a good cross section of diseases of the nervous system that might be encountered in any large general hospital. The introductory chapter deals in some detail with the histologic alterations occurring in the parenchyma and interstitial elements of the nervous system. From this point on the reader is not burdened with too much histologic detail. The main emphasis is on the "development, gross appearance, and ultimate fate" of the common lesions of the nervous system.

The author has succeeded in injecting enough clinical correlation to give the general reader proper perspective of the subject. The text is well organized and follows the usual plan found in most texts on the subject. The appendix consists of eleven pages of clinicopathologic aphorisms which the author has written as an aid in the clinical diagnosis of nervous diseases. The following is an example of one: "The relatively rapid development of a paraplegia with signs of inflammation (fever, leucocytosis, etc.) often indicates an extradural spinal abscess. Immediate surgical exploration is indicated if the patient is to be saved."

The text is well illustrated with two hundred photographs and drawings. The type is very readable and the book has been nicely prepared. It can be recommended to any reader desiring general pathologic information on the common diseases of the brain and spinal cord.

J G A, Jr

COLLEGE NEWS NOTES

NEW LIFE MEMBERS

Announcement is made of the following additional Life Members of the American College of Physicians

Dr Eben C Hill, Baltimore, Md
Dr James H Means, Boston, Mass

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members

Dr Jacob Gutman, F A C P, Brooklyn, N Y—Supplement to Gutman's Modern Drug Encyclopedia, Fourth, Second Series,
Dr Winthrop Wetherbee, Jr (Associate), Boston, Mass—1 book, "Medicine in the Outpatient Department",
Dr Miles J Breuer, F A C P, Lincoln, Nebr—1 reprint,
Dr Coyne H Campbell (Associate), Oklahoma City, Okla—5 reprints,
Dr Harry Halprin, F A C P, Caldwell, N J—1 reprint,
Dr D O N Lindberg, F A C P, DeCATur, Ill—1 reprint,
Dr James R Lisa, F A C P, New York, N Y—14 reprints,
Dr Harold C Lueth (Associate), Evanston, Ill—11 reprints,
Dr Wm deB MacNider, F A C P, Chapel Hill, N C—4 reprints,
Dr John I Marker, F A C P, Davenport, Iowa—1 reprint,
Dr Samuel S Paley (Associate), New York, N Y—3 reprints,
Dr Samuel A Shelburne, F A C P, Dallas, Texas—2 reprints

COMMITTEE ON NOMINATIONS

President William J Kerr on November 14, 1938, announced the appointment of Dr Donald J Frick, of Los Angeles, Calif, as a member of the Committee on Nominations to take the place of the late Dr Walter P Bliss, of Pasadena, Calif Dr Frick is an appointment from the Fellowship-at-large The other members of the Committee consist of

Dr James Alex Miller, New York City, *Chairman* (from the Board of Regents)
Dr D Sclater Lewis, Montreal (from the Board of Regents)
Dr Henry M Thomas, Jr, Baltimore (from the Board of Governors)
Dr Fred W Wilkerson, Montgomery, Ala (from the Board of Governors)

MARYLAND CHAPTER OF THE AMERICAN COLLEGE OF PHYSICIANS HOLDS MEETING, NOVEMBER 19, 1938

One of the largest and most successful State meetings of Fellows and Associates of the American College of Physicians was held at Baltimore, November 19, 1938, with Dr Henry M Thomas, Jr, Governor for Maryland, presiding Dr Sydney R Miller, ex-President and Regent of the College, took an active part in organizing the program, and at the dinner which followed the afternoon session he addressed the group on topics of especial interest concerning the present and future activities of the College The scientific program follows

- 1 Teratoma of the Mediastinum Surgical Treatment William F Rienhoff, Jr
 - 2 Regression of Retinitis in a Case of Arterial Hypertension James Bordley, III
 - 3 Parietal Lobe Syndrome with Motor Aphasia with Autopsy Findings Wendall Muncie
 - 4 Lymphoblastoma Simulating Hodgkin's Disease Henry M Thomas, Jr
 - 5 A Case of Malta Fever Charles W Wainwright
 - 6 Addison's Disease Treatment with Desoxy-Corticosterone Acetate George Thorn
 - 7 Type III Pneumonia Three Cases Treated with Anti-Pneumococcus Rabbit Serum Carmichael Tilghman
-

Under the Presidency of Dr James Alex Miller, F A C P, the New York Academy of Medicine conducted its Eleventh Annual GRADUATE FORTNIGHT, October 24–November 4, 1938 These meetings have become popular as concentrated postgraduate courses for physicians not only in the area of New York City, but from more distant points

Dr Charles F Tenney, F A C P and Governor of the College for Eastern New York, and Dr Mahlon Ashford, F A C P, acted as Chairman and Secretary, respectively, of the Graduate Fortnight Committee Among other members of the Committee were Dr Thomas T Mackie, F A C P, Dr Herman O Mosenthal, F A C P, and Dr Bernard S Oppenheimer, F A C P Dr Mackie also acted as the Chairman of the Committee on Clinics

The Fortnight was given over particularly to the subject of diseases of the blood and blood-forming organs Among invited guests were Dr George R Minot, F A C P, Professor of Medicine at Harvard University, Dr Cyrus C Sturgis, F A C P, Professor of Internal Medicine at the University of Michigan Medical School, Dr Russell L Haden, F A C P, Chief of the Medical Division of the Cleveland Clinic, and Dr Claude E Forkner, F A C P, Assistant Professor of Clinical Medicine at Cornell University Medical College Fellows and Associates of the College filled thirty-nine different appointments on the program

SECTIONAL MEETING, SOUTHERN ILLINOIS DISTRICT, AMERICAN COLLEGE OF PHYSICIANS

This year the annual meeting of the Fellows and Associates of the College from southern Illinois was combined with the Sixty-fourth Semi-Annual Meeting of the District Medical Society of Central Illinois, and was held at Decatur, November 15, 1938

The meeting began at seven-thirty in the morning with a number of selected surgical clinics followed by a clinico-pathological conference and a tumor conference The Decatur and Macon County Hospital provided a complimentary luncheon, after which the meeting adjourned to the Macon County Tuberculosis Sanatorium, where a motion picture, "Let My People Live," was shown

The program from two o'clock in the afternoon on was sponsored especially by Fellows of the College and consisted of the following

- "Complications and Sequelae of Coronary Occlusion"—Dean F Stanley (Associate), Decatur Discussion Dr Edgar M Stevenson, F A C P, Bloomington
- "Paget's Disease"—Dr M E Rose (Associate), Decatur Discussion Dr Harold Swanberg, F A C P, Quincy

- "Subdural Hematoma"—Dr O O Stanley, F A C P, Decatur Discussion Dr George Parker, F A C P, Peoria
- "Undulant Fever"—Dr C M Jack, F A C P, Decatur Discussion Dr Warner H Newcomb, F A C P, Jacksonville
- "Diagnostic Procedures in Tuberculosis"—Motion Picture
- "Pulmonary Tuberculosis—Demonstrations"—Dr D O N Lindberg, F A C P, Decatur Discussion Dr Robinson Bosworth, F A C P, East St Louis

In the evening there was a social gathering, and informal reception by the Macon County Medical Society, and dinner at the Hotel Orlando The address of the evening, "The Challenge to American Medicine," was delivered by Dr James D Bruce, F A C P and Regent of the College, Vice President in Charge of Postgraduate Education, University of Michigan

SECTIONAL MEETING, RHODE ISLAND MEMBERS OF THE COLLEGE

One of the largest gatherings of medical men in Rhode Island was held at the Memorial Hospital, Pawtucket, in connection with Interne Alumni Clinic Day under the Chairmanship of Dr John F Kenney, F A C P

Clinics by the staff were given in the morning and were attended by all the Rhode Island Fellows and Associates The afternoon program was turned over to the following members of the College

- "Coronary Insufficiency"—Dr William D Stroud, F A C P, Professor of Cardiology, University of Pennsylvania Graduate School of Medicine
- "Endocrine Therapy in the Treatment of Allergic Disorders"—Dr Harry Bond Wilmer, F A C P, Assistant Professor of Clinical Immunology, University of Pennsylvania Graduate School of Medicine
- "Acute Hepatic Cellular Disease"—Dr George Morris Piersol, F A C P, Vice Dean for Medicine, University of Pennsylvania Graduate School of Medicine

Included also on the afternoon program was Dr Alexander Randall, Medical Professor of Urology, University of Pennsylvania and the title of his speech was "Obstructive Uropathy"

Under the Presidency of Dr Elliott P Joslin, F A C P, Clinical Professor of Medicine, Emeritus, Harvard Medical School, and Medical Director of the George F Baker Clinic, New England Deaconess Hospital, the Inter-State Postgraduate Medical Association of North America held its Twenty-third Assembly in Philadelphia, October 31—November 4, 1938

Among contributions to the program by *Fellows* of the College were the following

- Diagnostic Clinic "Acute Coronary Occlusion"—Dr G Harlan Wells, Philadelphia, Pa
- Diagnostic Clinic "The Significance of Jaundice"—Dr Henry A Christian, Boston, Mass
- Diagnostic Clinic "The Treatment of Anemia"—Dr Russell L Haden, Cleveland, Ohio
- Address "The Therapeutic Value of Blood Transfusions"—Dr Cyrus C Sturgis, Ann Arbor, Mich

- Address "Obscure Fevers as Diagnostic Problems"—Dr George Blumer, New Haven, Conn
- Diagnostic Clinic "Diagnostic Significance of Pain"—Dr Frederick J Kalteyer (Associate), Philadelphia, Pa
- Therapeutic Clinic "The Treatment of Dehydration and Edema"—Dr James H Means, Boston, Mass
- Address "Immediate and Ultimate Prognosis in Heart Disease"—Dr Paul D White, Boston, Mass
- Address "Diagnosis and Treatment of Bronchogenic Carcinoma"—Dr Arthur C Christie, Washington, D C
- Diagnostic Clinic "Diabetes Mellitus from an Endocrinological Viewpoint"—Dr Elliott P Joslin, Boston, Mass
- Address "A Medical Appraisal of the Surgery of Pulmonary Tuberculosis"—Dr William S Middleton, Madison Wis
- Diagnostic Clinic "Non-Organic Disorders of the Digestive Tract"—Dr Alfred Stengel (Master), Philadelphia, Pa
- Diagnostic Clinic "Somatic Complaints in the Neuroses, Case Presentations"—Dr Peter T Bohan, Kansas City, Mo
- Diagnostic Clinic "Hodgkin's Disease"—Dr Warfield T Longcope, Baltimore, Md
- Address "The Object and the Value of Preoperative and Postoperative X-Ray Treatment in Carcinoma of the Breast"—Dr George E Pfahler, Philadelphia, Pa
- Address "The Prognosis and Treatment of Rheumatic Heart Disease"—Dr Fred M Smith, Iowa City, Iowa
- Address "Pellagra"—Dr John H Musser, New Orleans, La
- Diagnostic Clinic "Carcinoma of the Larynx with Special Reference to End Results"—Dr Louis H Clerf, Philadelphia, Pa
- Diagnostic Clinic "The Differential Diagnosis of Diseases of the Chest and Abdomen"—Dr David Riesman, Philadelphia, Pa
- Address "The Present Status of Our Knowledge of the Suprarenal Cortical Hormone"—Dr George A Harrop, New Brunswick, N J
- Address "Studies in Growth—Precocious and Malignant"—Dr Leonard G Rowntree, Philadelphia, Pa
- Address "Influenzal Pneumonias Observations on Their Pathological Features and Clinical Characteristics"—Dr Robert G Torrey, Philadelphia, Pa

Dr Edward L Bortz, F A C P and Governor of the College for Eastern Pennsylvania, Philadelphia, was elected November 16 as President-Elect of the Philadelphia County Medical Society

ANALYSIS OF CIRCULATION, "ANNALS OF INTERNAL MEDICINE"

The Executive Offices of the College recently completed a detailed analysis of the circulation of the ANNALS OF INTERNAL MEDICINE, using the circulation of the June, 1938, issue. The circulation of the ANNALS is not restricted to members of the American College of Physicians alone, but goes to many other physicians and institutions.

For the interest of members of the College, the following specialty and regional analyses are reproduced

SPECIALTY ANALYSIS

(Volume XI, No 12)

	<i>Primary Specialty</i>	<i>Secondary Specialty</i>
INTERNAL MEDICINE	2,518	54
Allergy	10	116
Arthritis	5	40
Aviation and Military Medicine	8	17
Cardiology	56	398
Diseases of the Chest	49	122
Endocrinology	7	51
Gastro-enterology	43	208
Hematology and Blood Diseases	3	20
Immunology and Preventive Medicine	7	12
Medical Education and Administration	22	23
Metabolic Diseases	11	112
Physical Therapy		16
Research	8	39
Tropical Medicine	5	23
Tuberculosis	80	94
Total sub-specialties	314	1,291
TOTAL, INTERNAL MEDICINE	2,832	1,345
GENERAL MEDICINE	457	31
NEUROLOGY AND PSYCHIATRY	191	128
MEDICAL LIBRARIES AND SOCIETIES	164	
HOSPITALS	148	
PEDIATRICS	145	21
PATHOLOGY, CLINICAL PATHOLOGY	133	93
RADIOLOGY, ROENTGENOLOGY	97	23
EDITORS AND PUBLISHERS	69	
MEDICAL MANUFACTURERS	41	
DERMATOLOGY, SYPHILOLOGY	38	38
PUBLIC HEALTH, STUDENT HEALTH	38	18
SURGICAL SPECIALTIES	33	8
MISCELLANEOUS	95	48
NO SECONDARY SPECIALTY GIVEN		2,728
	4,481	4,481

REGIONAL ANALYSIS

(Volume XI, No 12)

Middle Atlantic States	1,609
Central States	1,176
Southern States	610
Western States	492
New England States	329
U S Possessions	49
TOTAL, UNITED STATES	4,265
Canada	95
Europe	57
Asia	23
South America	16
Mexico	7
Other Countries	18
	4,481

Dr Herman M Baker, F A C P, Evansville, President of the Indiana State Medical Association, has appointed a committee to study the present national situation relating to the future practice of medicine

Dr Roscoe H Beeson, F A C P, Muncie, is among the appointees

Construction recently was started on a new five-story, southern colonial style medical building at the University of North Carolina in Chapel Hill. Administrative offices, the division of public health, departments of anatomy, biologic chemistry, pathology, pharmacology, physiology, bacteriology, public health, and laboratories, seminar rooms and a large library will be housed herein. Dr. William deB. MacNider, F A C P, is the Dean of the Medical School.

Dr. Frank H. Krusen, F A C P, Rochester, Minn., was recently installed as President of the American Congress on Physical Therapy.

Dr. Thomas Parran, F A C P, Surgeon-General of the U. S. Public Health Service, was one of the principal speakers at the dedication exercises for a new library building of Abbott Laboratories, pharmaceutical manufacturers, in North Chicago, Ill., October 7. The dedication of this building marked the fiftieth anniversary of this organization.

Dr. Burton R. Corbus, F A C P, Grand Rapids, Mich., was made President-Elect of the Michigan State Medical Society at its last annual meeting.

Dr. Henry A. Luce, F A C P, Detroit, Mich., was installed as President.

The Michigan State Medical Society has initiated annual convocations for certification in graduate education. The first convocation was held during September, and was established to certify those physicians who attended special sessions in graduate education for four years. Physicians who complete the first term of attendance at these courses of graduate lectures will be indicated as "associate fellows," and those who complete a second term will be indicated as "fellows."

At the first convocation, more than five hundred physicians received certificates. Physicians may participate either in the extra-mural courses or in the intramural courses offered at the University of Michigan Medical School and Wayne University College of Medicine.

Dr. Henry A. Luce, F A C P, Detroit, presided at the convocation, and Dr. James D. Bruce, F A C P, Ann Arbor, Vice President in Charge of Graduate Education at the University of Michigan, delivered an address on "The Challenge of Medical Service."

Dr. Joseph C. Doane, F A C P, Philadelphia, is Editor of "Modern Hospital." A special issue last September marked the twenty-first anniversary of its founding.

Dr. Philip I. Nash, F A C P, Brooklyn, President-Elect of the Medical Society of Kings, and Dr. John P. Peters, Professor of Medicine at Yale University School of Medicine, New Haven, were the principal speakers at a symposium on "The Future of American Medicine," October 21, under the auspices of the Interne Council of America.

Dr. Thomas T. Mackie, F A C P, New York, N. Y., and Dr. Robert L. Levy, F A C P, New York, N. Y., were among the guest speakers at the seventh Post Graduate Medical Assembly of South Texas held at Houston in November.

Dr. Andrew D. Hart (Associate) has been appointed Professor of Clinical Medicine and Director of Student Health at the University of Virginia, Charlottesville.

The Tenth International Congress of Military Medicine and Pharmacy will be held in Washington, D C, May 7-15, 1939, under the Presidency of Major General Charles R Reynolds, F A C P, Surgeon-General of the U S Army. Invitations to participate have been sent to all parts of the world by the President of the United States, and many countries have already sent acceptances.

Under the leadership of Dr Walter L Treadway, F A C P, Assistant Surgeon-General of the U S Public Health Service, a symposium on mental health will be presented before the Section on Medical Sciences of the American Association for the Advancement of Science, Richmond, Va, December 28-30.

The American Psychiatric Association, the U S Public Health Service, the Mental Hospital Survey Committee and the National Committee for Mental Hygiene are assisting. It is said that this is the first time in the history of American psychiatry that the subject of mental health has received special attention as a major topic on the program of this large scientific body, which has an active membership of over nineteen thousand, and an affiliate membership of three-quarters of a million.

Dr Samuel M Feinberg, F A C P, Chicago, addressed the Tippecanoe County Medical Society at La Fayette, Ind, November 8, on "Newer Developments and Common Misconceptions of Allergy."

A meeting of the Maine members of the American College of Physicians was held at the Maine General Hospital in Portland on December 2. The scientific program follows:

- 1 Chronic Non-tuberculous Pulmonary Disease, with motion pictures—Dr Francis J Welch, Portland
- 2 Observations in Coronary and Renal Injection Studies—Dr Julius Gottlieb, Lewiston
- 3 Laboratory Diagnosis of Typhoid Fever—Dr Mortimer Warren, Portland
- 4 Bachman Skin Tests and Eosinophil Counts in Individuals Who Have Previously Suffered from Trichinosis—Dr Richard S Hawkes, Portland
- 5 Cardiac Infarction Involving the Lateral Wall of the Left Ventricle—Dr E H Drake, Portland

POST-CONVENTION TOUR TO MEXICO CITY

(Consult page 16 of the Advertising Section for detailed announcements concerning this Post-Convention Tour following the New Orleans Session of the College, March 27-31, 1939.)

Mexico City has been traditionally the center of national life since long before the Spaniards discovered the American Continent. It is today the center of the cultural, social, economic and political life of Mexico. Mexico City is to the Mexicans what Paris is to the French.

The Mexico City of today that you will see is entirely different from the original crude village that was its seed, and from the proud capital of the Aztecs that Cortez saw as he gazed down into the valley from the heights above. The original city was razed to the ground and a new one built in its place by Cortez, in the second, and greatest phase of his career, that of Colonizer. Many of those buildings, now several centuries old, you will see on your tour around the city.

In Mexico City centuries rub elbows. One's imagination is stimulated by its high lights and shadows. A modern assembly plant turns out tractors and six miles away the Indian is turning over the top soil with the help of a wooden plow, just as

his forebears did centuries ago. You admire the vast Palace of Fine Arts in all its modern marbled magnificence and within a stone's throw you will find a dozen buildings dating back to the 16th century. The fashionable "sub-deb" with a frock typifying "le dernier cri" may be walking down Madero Avenue and actually rubbing elbows with a group of "pilgrims" from some remote highland village, who have been frightened nearly out of their brown skins by the rush of the city's street traffic, where for twenty years not a horse drawn vehicle has turned. You see so many centuries in one day that it takes weeks to digest it.

The National Cathedral, begun in 1525 on the site of the principal pagan temple of the Aztecs and completed in 1575, recognized now as the oldest and finest religious structure in any of the Americas, the National Palace, built, by order of the King of Spain, to replace the burnt and pillaged palace of Montezuma, in 1692, the National Museum where the ancient monoliths, pagan idols, and sacrificial stones of a forgotten race have been preserved, the National Pawn Shop, conceived and founded a full year before the American Revolution by a charitable man to lend money to the poor at low interest rates, the National University, scattered about the city and built, by the royal order of Charles V of Spain, a full century before the founding of Harvard, the House of Tiles and Iturbide Palace, on the Avenida Madero, in the heart of the modern business section, two places of unusual interest, the Paseo de la Reforma, Mexico City's "Fashion Lane" and streets of magnificent homes, that leads to the entrance to Chapultepec Park, and Chapultepec Castle, former home of the Presidents of Mexico and former palace of the Emperor.

Venturing afield in our explorations of this ancient and interesting country we shall see the Pyramids of San Juan Teotihuacan. These black, brooding monuments, that have been unearthed in the last few years, are of an indeterminate age and origin, but have been guessed by archeologists to antedate the Pharaohs' Tombs in the Valley of the Nile. The biggest of the group, the Pyramid of the Sun, is larger at the base than any of the Egyptian Pyramids and almost as tall. Queer carvings and symbolic writings decorate the interior chambers and set the world to guessing at their meanings, at the minds that conceived them and the hands that fashioned them untold centuries ago. Engineers who have seen the structure have marveled at the mathematical exactness of their erection, and have scratched their heads in wonder over what manner of man could have transported the huge blocks and set them one upon another by no other agency than manpower. They are a glimpse into the closed book of the past, a definite proof that man had a knowledge of art and the exact sciences long before our own civilization came into being.

Cholula was, at the time of the Conquest, the religious center of the Aztec Empire. It was here that Cortez, in his righteous wrath against the heathen practices of the high priests, conquered the city and set about to fulfill his vow that he would erect a church for every day in the year. There are over three hundred of them, beautiful examples of the artistic nature that the Cholulans must have had, for it was they and their descendants who built them under the lash of their Spanish masters. The Cathedral is regarded as the most beautiful religious edifice south of the Rio Grande.

Puebla, the third largest city in the Republic, is often called the "City of Churches." It is also the home of the renowned Talavera pottery and tile industry, and many of its homes and buildings are roofed and floored with the colorful and decorative material.

Cuernavaca is an exceedingly picturesque town with a delightful air of antiquity. Cortez built a palace here in 1530 and we shall see the same magnificent panorama that delighted him. The Cathedral was built in 1529 and Mass was said there a hundred years before the landing of the Pilgrims. You will wander through the plaza, the market, and the dozens of shoe shops in one of which you will probably buy a pair of woven leather sandals for which Cuernavaca is famous. Of course,

you will see Diego Rivera's frescos in Cortez' Palace and wander through the Borda Gardens which witnessed many of Maximilian's and Carlotta's tragic days

The Monastery at Acolman looks like a massive fortress, but its facade and cloisters are arresting. The bizarre frescos painted hundreds of years ago will captivate you, though the ravages of time and flood have been unkind to some of them.

The present Basilica at Guadalupe which dates from 1709 was built in honor of the Virgin of Guadalupe, patron saint of Mexico and Latin-America. Here we may see a "pilgrimage" from some nearby or remote village, offering tribute to the beloved Virgin. The legend of her apparition before the humble Indian, Juan Diego, has gripped the heart and imagination of the Mexican people. There she is perpetually enshrined.

Puebla is one of the oldest cities in Mexico and one which most perfectly retains its colonial atmosphere. Its strategic position as key to the capital made it the center of strife for years. Puebla is a gem with its well laid out streets, its overpowering churches whose multicolored domes glisten in the Mexican sunlight and its famed Talavera pottery and tiles, which industry was brought over by the conquerors.

Xochimilco, the Floating Gardens, is a unique and beautiful combination of lakes, canals and gardens. We ride the canals in flat bottom boats, plying our way among the flower laden islands that have been formed by nature from floating masses of twigs and branches covered with earth. It is a rare and lovely experience to ride these shaded, flower-lined waterways whose quiet is disturbed only by the birds. No matter which way you look you see flowers on island gardens, pleasant looking Indians balanced in canoes offering flowers for sale or with musicians singing and strumming guitars. No streets and no houses face the canals and you will be punting along a world of islands and canals with everybody happy and gay.

OBITUARY

DOCTOR KALLMAN MEYER DAVIDSON

With the death of Dr. Kallman Meyer Davidson, F.A.C.P., Boston, Mass., in his seventy-sixth year, on July 22, 1938, there passed from our midst a striking personality embodying qualities which give a place of honor to the family physician. Cultured, keeping zealously abreast with medical progress, endowed with a good stock of common sense and a fine sense of humor, he was the beloved advisor of three generations.

He had been in active medical practice for over half a century, and since 1891 in Boston. He brought to our community at that time a combination of the best in Russian-Jewish culture with the thorough training in medicine afforded in Germany in the last quarter of the nineteenth century, under the direct influence of men like Hermann, Virchow, Koch, Ehrlich, Naunyn and Minkowski. Thus prepared and with a naturally keen and inquisitive mind he was from the first a pioneer in raising the standards of medical practice especially among the immigrant part of our population. This was recognized not only by the people he served but also by the leaders of the profession, as shown by the friendship in those days of such men as Frederick C. Shattuck, Maurice H. Richardson and Reginald H. Fitz.

Particularly noteworthy was his active leadership in developing hospital service among his people here in Boston. In 1903 he was the prime mover in the organization of the Mount Sinai Dispensary, and in 1913 he was a leader in the founding of the Beth Israel Hospital, which has since developed into an outstanding institution.

Doctor Davidson was an indefatigable worker and always considered the practice of medicine as clinical research. He loved books and read extensively the medical literature. Ever young in spirit and in his interests he was a familiar figure at medical gatherings, and found great pleasure in his membership in the American College of Physicians.

He was a man of great fortitude and bore most courageously two calamities in his life—the loss of his beloved wife and more recently the untimely death of his brilliant son, Dr. Percy B. Davidson.

His memory will long be cherished.

HYMAN MORRISON, M.D.

DOCTOR ARTHUR EVERETT AUSTIN

Dr. Arthur Everett Austin, F.A.C.P., Boston, Mass., died at Windham, N.H., August 22, 1938, aged, 77 years.

Dr. Austin was born in 1861. After securing an A.B. degree from Bowdoin College in 1883, he went on to the Harvard University Medical School, where he received a degree of M.D. in 1887. In the same year he also received a degree of A.M. from Bowdoin College. In 1895 and 1897, he pursued postgraduate work in biochemistry at the University of Berlin, and in 1904–05 he took postgraduate work in gastro-enterology at the University of Vienna. Later he held the chair of Professor of Biochemistry at the University of Virginia and also at the University of Texas, and at his death was Professor Emeritus of Theory and Practice of Medicine at the Tufts College Medical School in Boston. He has served on the medical staffs of the Mt. Sinai Hospital and the Massachusetts General Hospital in Boston, and served as Major in the Medical Corps, U.S. Army, during the World War. His interest was primarily in diseases of the digestive tract, and he wrote various papers concerning such diseases. He was a member and former councillor of the Massachusetts Medical Society, member of the American Medical Association, and had been a Fellow of the American College of Physicians since 1920.

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts

DOCTOR JAMES ALLEN JACKSON

Dr. James Allen Jackson, F.A.C.P., died December 1, 1938, of leukemia. For the past eighteen years he was Superintendent of the Danville State Hospital for Mental Diseases. He was born in Upatoi, Ga., attended the University of Georgia and was graduated from Jefferson Medical College.

of Philadelphia in 1906. He served as Resident Pathologist at the Philadelphia General Hospital, 1906 to 1908, and as Pathologist to the Central Indiana Hospital for the Insane from 1908 to 1910. He returned as Chief Resident Physician to the Philadelphia Hospital for Mental Diseases, where he served from 1910 to 1920. In addition to being Superintendent of the Danville State Hospital, he was Consultant to the George F. Geisinger Memorial Hospital, Bloomsburg Hospital and Williamsport Hospital, also Consultant-at-large in Mental Hygiene to the United States Public Health Service. He was a member of the Montour County Medical Society, Pennsylvania State Medical Society, Philadelphia Psychiatric Society, Philadelphia Neurological Society, American Medical Association, American Psychiatric Association, and had been a Fellow of the American College of Physicians since 1923.

Dr. Jackson wrote extensively on mental hygiene, and organized a chain of mental hygiene clinics in central Pennsylvania to serve those unable to be admitted to Danville. He was 33d degree Mason, and a member of the Editorial Staff of the Modern Hospital Magazine.

Dr. Jackson was a tireless worker. In addition to his professional skill and energy, he enjoyed the friendship and esteem of a large circle of friends. The profession and the community have, in his death, lost an outstanding leader.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DOCTOR JOSEPH MILLEN KING

Joseph Millen King (Fellow), Los Angeles, died October 27th on his 66th birthday. He was sitting in his automobile at the time about to leave his home for a professional call. Though he had had a coronary disease and knew the possibilities he kept working whenever he felt able.

Dr. King was born in the Parish of St. James, New Brunswick. He early moved to Pennsylvania, doing his pre-medical work at Geneva College. In 1889 he moved to San Diego. After teaching school for a couple of years he entered the College of Medicine of the University of Southern California, where he was graduated in 1895. Dr. King was a member of his County and State Associations and a Fellow of the A.M.A. He was a past President of the Los Angeles County Medical Association, the Southern California Medical Association and the California State Medical Association. He was a past President of the Los Angeles Clinical and Pathological Society of which he was also a founder member. He was a Clinical Professor of Medicine in the Medical School of the University of Southern California at the time of his death.

Dr. King did graduate work at Johns Hopkins in 1904 and at Berlin, Munich and Vienna in 1912-13. Throughout his professional life Dr. King was a member of the Staff of St. Vincent's Hospital, at one time being

Chairman of the Staff He was also a member of the Staff of several other Los Angeles Hospitals In all his professional circles his friendliness, forceful personality and sage counsel were highly valued He was a fine man and a good physician whose memory will live long after him

EGERTON CRISPIN, M D , F A C P ,
Regent

DOCTOR DAVID R CLARK

Dr David R Clark (Associate), of Detroit, Michigan, died July 3, 1938, after a year's illness

Born January 26, 1874, in Port Clinton, Ohio, he was graduated from the University of Michigan Medical School in 1895 After several years' practice in Niles, Michigan, he came to Detroit where he specialized in psychiatry

For over forty years, Dr Clark had been Senior Medical Officer of St Joseph's Retreat, Dearborn, and for twenty years of the psychopathic department of Detroit Receiving Hospital He was past president of the Detroit Society of Psychiatry, and a member of the American Psychiatric Association At the time of his death, he was one of the elder of the Detroit group of psychiatrists

Besides his institutional appointments, Dr Clark had a large practice of devoted patients An able psychiatrist, he was also an earnest student of sociology He was active in advocating hospital additions and improvements in the care of mental cases in this state

Greatly beloved by the profession for his keen clinical insight, warm friendship to his friends and loyalty to his ideals, Dr Clark will be greatly missed by the physicians and the public whom he so ably served

HENRY R CARSTENS, M D , F A C P ,
Governor for Michigan

DOCTOR FELIX P CHILLINGWORTH

Doctor Felix P Chillingworth (Fellow), aged 55 years, died at his summer home in Concord, Massachusetts, on June 29, 1938, after a serious illness of eight months

Doctor Chillingworth was a graduate of the Yale School of Medicine in 1907, and practiced medicine in Hoddam, Connecticut, for four years, but his aptitude for research and teaching found an outlet when he went into the Department of Physiology at Kansas University in 1912, and then in 1913 to Tulane University in New Orleans where until 1919 he was Assistant Professor of Physiology During the years of the war, in addition to his medical teaching, he was physician to the Louisiana Leper Colony at Carville which later was taken over by the United States Government In 1919 he became Professor of Physiology in the Tufts Medical and Dental Schools

in Boston, Massachusetts, and in 1929 Professor of Pharmacology in same schools

His research publications have been extensive both in British and American medical journals

Doctor Chillingworth was a great lover of travel and in his later years took up etching as a hobby. He was a member of various social clubs in Massachusetts, Connecticut and Louisiana, and held membership in many medical and scientific organizations

He is survived by his widow, Gertrude Smith Chillingworth, two sons, William Felix Chillingworth and Philip Oliver Chillingworth and a sister, Lillie M. Bryant

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts

DOCTOR LOUIS M. WARFIELD

Dr. Louis M. Warfield, of Milwaukee, Wisconsin, died September 1938. Dr. Warfield was born in Savannah, Georgia, in 1876, received A.B. degree in 1897, and M.D. degree in 1901 from Johns Hopkins University. Immediately after graduating, he went to the Rockefeller Institute, where he did work in pathology. Following this, he studied abroad for a year and one half, after which he returned to Savannah, and entered practice. He then went to St. Louis, where he was Secretary of the American Tuberculosis Association, and from St. Louis, he came to Milwaukee, and was in charge of the medical service at the Milwaukee County Dispensary and Hospital. During the war, he held a commission as Major, and was stationed at Jefferson Barracks, Missouri, where he was chief of the medical service. For two and one half years (1922-1924), he was Professor of Medicine at the University of Michigan. Following his resignation, he spent several months abroad, and again returned to practice medicine in Milwaukee with his special interest centered in cardiovascular diseases. In 1925, Dr. Warfield established the Milwaukee Internists Club, which is now the Milwaukee Society of Internal Medicine. He was a member of the American Medical Association, the American Association of Physicians, the American College of Physicians, was a past president of the Milwaukee Academy of Medicine, an emeritus member of the Central Society for Clinical Research, a member of the Chicago Internists Society, a past editor of the *Wisconsin Medical Journal*, and at his death president of the Wisconsin Anti-Tuberculosis Association.

ROCK SLEYSER, M.D., F.A.C.P.,
Governor for Wisconsin

